PB81-117327

Ambient Water Quality Criteria for Arsenic

(U.S.) Environmental Protection Agency
Washington, DC

Oct 80

U.S. Department of Commerce
National Technical Information Service
NTIS

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards
Criteria and Standards Division
Washington DC 20460

EPA 440/5-80-021
October 1980

PB81-117327

EPA

Ambient Water Quality Criteria for Arsenic

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

TECHNICAL REPORT DATA

(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO. PB81 117327
4. TITLE AND SUBTITLE Ambient Water Quality Criteria for: Arsenic		5. REPORT DATE October, 1980 6. PERFORMING ORGANIZATION CODE NTISEPAOWP
7. AUTHOR(S) Environmental Criteria and Assessment Office		8. PERFORMING ORGANIZATION REPORT NO. EPA-440/5-80-021
9. PERFORMING ORGANIZATION NAME AND ADDRESS Office of Water Regulations and Standards Criteria and Standards Division U.S. Environmental Protection Agency Washington, D.C. 20460		10. PROGRAM ELEMENT NO. 11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Same as box 9		13. TYPE OF REPORT AND PERIOD COVERED 14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

Supersedes draft document PB 292 420

16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Arsenic. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT For Public Release	19. SECURITY CLASS *(This Report)* Unclassified	21. NO. OF PAGES
	20. SECURITY CLASS *(This page)* Unclassified	22. PRICE

EPA Form 2220-1 (9-73)

AMBIENT WATER QUALITY CRITERIA FOR
ARSENIC

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

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ACKNOWLEDGEMENTS

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CRITERIA DOCUMENT

ARSENIC

CRITERIA

Aquatic Life

For freshwater aquatic life the concentration of total recoverable trivalent inorganic arsenic should not exceed 440 µg/l at any time. Short-term effects on embryos and larvae of aquatic vertebrate species have been shown to occur at concentrations as low as 40 µg/l.

The available data for total recoverable trivalent inorganic arsenic indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 508 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of trivalent inorganic arsenic to sensitive saltwater aquatic life.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of arsenic through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 22 ng/l, 2.2 ng/l, and 0.22 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 175 ng/l, 17.5 ng/l, and 1.75 ng/l, respectively.

INTRODUCTION

Arsenic is a naturally occurring element often referred to as a metal, although chemically classified as a metalloid. Arsenic and its compounds are used in the manufacturing of glass, cloth, and electrical semiconductors, as fungicides and wood preservatives, as growth stimulants for plants and animals, as well as in veterinary applications (U.S. EPA, 1976b). The United States consumes half of the world production of arsenic, or about 37,500 tons per year, and produces about 18,000 tons per year itself. The principal emission source for arsenic in the United States is thought to be coal-fuel power plants, which emit approximately 3,000 tons of arsenic per year (Nelson, 1977).

Environmental concentrations of arsenic have been reported at 5 mg per kg in the earth's crust (U.S. EPA, 1976a). Arsenic is found also in air and in all living organisms. Analysis of 1,577 U.S. surface waters showed arsenic to be present in 87 samples, with concentrations ranging from 5 to 336 µg/l and a mean level of 64 µg/l (Kopp, 1969). Bowen (1966) reported 3.0 µg/l in sea water.

A member of Group VB of the periodic table, arsenic has five electrons in its outer shell, giving rise to the oxidation states of +5, +3, 0, and -3. Arsenic as a free element (0) is rarely encountered in natural waters. Soluble inorganic arsenate (+5) predominates under normal conditions since it is thermodynamically more stable in water than arsenite (+3) (Ferguson and Gavis, 1972). Elemental arsenic is a gray, crystalline material with a molecular weight of 74.92, a density of 5.727, a melting point (at 28 atmospheres) of 817^{o}C, and a boiling point (sublime) of 613^{o}C (Weast, 1975). The low toxicity of elemental arsenic is attributed to its virtual insolubility in water or in the body fluids (U.S. EPA, 1976b).

A distinction should be made between different means of classifying arsenic compounds. The compounds of arsenic may be classified according to the oxidation state of arsenic (As^{3-}, As^{3+}, and As^{5+}) and according to whether or not arsenic is in the organic form (i.e., the arsenic atom is covalently attached to at least one carbon atom).

Conditions of low pH, low Eh (standard oxidation-reduction potential) and low dissolved oxygen in water favor the formation of lower oxidation state arsenicals such as arsenite (+3) and arsine (-3) whereas more basic, oxygenated waters result in an increase in the percentage of arsenic present in the pentavalent state. The reducing action of certain organisms may also cause arsenite to be the predominate form. In waters of high organic content, a considerable amount of arsenic may be bound to colloidal humic matter (Ferguson and Gavis, 1972).

Both arsenate and arsenite can be removed from the water column by co precipitation or adsorption onto iron oxides (LaPeintre, 1954; Gupta and Ghosh, 1953). Arsenate species can also be removed by adsorption onto aluminum hydroxide and clays, while arsenite is readily adsorbed onto metal sulfides (Ferguson and Gavis, 1972).

Oxidation of arsenite to arsenate occurs slowly at neutral pH (faster in strongly acid or alkaline solutions), while methylation of arsenic to methyl and dimethylarsine by methanogenic bacteria is known to occur (McBride and Wolfe, 1971).

Arsine (AsH_3) and its methyl derivatives are the most acutely toxic compounds of arsenic. However, they do not occur in drinking water or in ambient water. Human exposure has occurred only through generation of these compounds in occupational settings. Thus, arsine compounds are not further considerated in this document.

The organics, which are not naturally occurring, are the largest group of arsenic compounds. The two most common organic arsenic compounds are the arsonic acids, $R\text{-}AsO\text{-}(OH)_2$, and the arsinic acids, R,R'-AsO-OH, where R and R' refer to a variety of organic (alkyl) groups (U.S. EPA, 1976b). The organic arsenic compounds considered to be of environmental importance are those containing methyl groups, the aromatic arsenic derivatives employed as feed additives and in veterinary medicine, and others which may have importance in biological systems (U.S. EPA, 1976a).

Arsenic forms a complete series of trihalides, while arsenic (V) fluoride is the only simple pentahalide known. All of the arsenic halides are covalent compounds that hydrolyze in the presence of water (Standen, 1967). Additional information on inorganic arsenic compounds is given in Table 1.

TABLE 1

Properties of Some Inorganic Arsenic Compounds*

Compound	Formula	Water Solubility	Specific Properties
Arsenic trioxide	As_2O_3	12×10^6 µg/l @ 0°C 21×10^6 µg/l @ 25°C	Dissolves in water to form arsenious acid (H_3AsO_3: $K = 8 \times 10^{-10}$ @ 25°C)
Arsenic pentoxide	As_2O_5	$2,300 \times 10^6$ µg/l @ 20°C	Dissolves in water to form arsenic acid (H_3AsO_4: $K_1 = 2.5 \times 10^{-4}$ $K_2 = 5.6 \times 10$ $K_3 = 3 \times 10^{-13}$)
Arsenic hydride (arsine)	AsH_3	20 ml/100 g cold water	This compound and its methyl derivatives are considered to be the most toxic.
Arsenic (III) sulfide	As_4S_6	520 µg/l @ 18°C	Burns in air forming arsenic trioxide and sulfur dioxide; occurs naturally as orpiment.
Arsenic sulfide	As_4S_4		Occurs naturally as Realgar.
Arsenic (V) sulfide	As_4S_{10}	1,400 µg/l @ 0°C	

*Source: Standen, 1967; U.S. EPA, 1976a,b

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Aquatic Life Toxicology*

INTRODUCTION

Arsenical compounds are found in all living organisms including those in aquatic systems. Although important sources of arsenic in the environment are industrial (Nelson, 1977; Fowler, 1977), such as smelters of nonferrous ores and coal-fired power plants using arsenic-rich coal, substantial arsenic contamination of water can also occur from the improper use of arsenical pesticides such as sodium arsenite which is often used as an aquatic herbicide.

The chemistry of arsenic is quite complex, consisting of chemical, biochemical, and geochemical reactions which together control the amount of dissolved arsenic concentrations in aquatic systems. A cycle for arsenic in natural waters has been diagrammed in an extensive review by Ferguson and Gavis (1972).

Arsenic is stable in water in four oxidation states (+5, +3, 0, -3) as both inorganic and organometallic species and in dissolved and gaseous states. Common arsenic species are arsenate, arsenite, methanearsonic acid and dimethyl arsenic acid (cacodylic acid). Arsenic as the free element (0) is rarely encountered in water but appears to be thermodynamically stable at lower Eh (standard oxidation reduction potential) values. At very low Eh, AsH_3 (arsine, -3) may be formed which is only slightly soluble. Arsenic sulfides have low solubilities and occur as stable solids at pH values below 5.5 and lower Eh conditions. Arsenite (+3) may also be present if the Eh is less than 0.1V. Arsenic (+3) has a strong affinity for sulfur and readily adsorbs or coprecipitates with metal sulfides.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of the appropriate table are calculations for deriving various measures of toxicity as described in the Guidelines.

In aerobic water, reduced forms of arsenic tend to be oxidized to arsenate (+5), the predominant form in these waters. The rate of oxidation of arsenite to arsenate by oxygen is slow at neutral pH, but proceeds measurably in several days in strongly alkaline or acidic conditions (Ferguson and Gavis, 1972). This oxidation, however, probably never proceeds to completion. Arsenate can coprecipitate with or adsorb on hydrous iron oxides and form insoluble precipitates with calcium, sulfur, aluminum, and barium compounds (Holm, et al. 1979). Arsenate is chemically similar to phosphate and may be enriched in phosphate minerals, although arsenic affinity to iron is predominant. The adsorption of arsenate by metal oxides and the formation of arsenic sulfide appears to remove arsenic from solution to the sediments and prevent high arsenic concentrations from being present in solution. Studies by Holm, et al. (1979) and others on the heterogeneous interactions of arsenic in aquatic systems indicate that arsenate is more strongly absorbed to sediments than are other arsenic forms. Generally, adsorption processes are very dependent on arsenic concentration, sediment characteristics, pH, and ionic concentration of other compounds. Arsenic can be removed from the sediments by volatilization and recycled in the water.

Inorganic arsenic can be converted to organic alkyl arsenic acids (+3 and +5) and to methylated arsines (-3) under anaerobic conditions by fungus, yeasts and bacteria, although biomethylation may occur under aerobic conditions as well.

Little is known about the mechanism of arsenic toxicity to aquatic organisms; however, arsenic readily forms kinetically stable bonds to sulfur and carbon in organic compounds. Like mercury, arsenic (+3) reacts with sulfhydryl groups of proteins; enzyme inhibition by this mechanism may be the primary mode of arsenic toxicity. Arsenate does not react with sulfhydryl groups as readily but may uncouple oxidative phosphorylation (Anderson, 1979).

Although considerable information has been published on the effects of arsenic on freshwater organisms, knowledge of its toxicity is less than complete since much of the work has been devoted to monitoring or field assessment studies or were studies that contained information that was not useful for deriving a water quality criterion. Virtually no data on chronic effects of arsenic on fish species exist, and only one invertebrate chronic test was found acceptable. Only two references dealing with arsenic bioconcentration by freshwater species accurately reported exposure concentrations or calculated useful bioconcentration factors.

The arsenic data base for saltwater organisms is inadequate to assess comparative sensitivity among a variety of organisms and their life stages or to assess the importance of water quality parameters such as salinity to arsenic toxicity. In addition, these data do not distinguish differences, if any, among various oxidation states.

The present data base for arsenic is separated into trivalent inorganic arsenic, pentavalent inorganic arsenic, and other arsenic compounds since the majority of toxicity tests were conducted with the trivalent form, particularly sodium arsenite, and because toxicity may be related to the form of arsenic present in solution. All results are expressed in terms of arsenic, not as the compound.

EFFECTS

Acute Toxicity

Seven acute tests with freshwater invertebrate species have been reported with trivalent inorganic arsenic and all were tested with sodium arsenite (Table 1). Only one (U.S. EPA, 1980) was a flow-through test with measured concentrations; the others were static tests with unmeasured concentrations. Crustaceans, comprised of three cladoceran and one scud species, showed some variation among species but were more than four times more sensitive than a stonefly species, an aquatic insect. The range of acute values for crustaceans was 812 to 5,278 µg/l. Daphnia magna appeared to be the most tolerant cladoceran although it was difficult to compare sensitivities due to the small data base. All crustacean species were more than twice as sensitive to trivalent inorganic arsenic as were the fish species tested. Stonefly sensitivity was within the range of sensitivity of fish based on 12 acute tests with fish.

The acute toxicity of trivalent inorganic arsenic to freshwater fishes is also summarized in Table 1. One-half of the tests were static with unmeasured concentrations and the others were flow-through tests with measured concentrations. Seven fish species are represented and sodium arsenite was used in all tests. Rainbow trout and brook trout were the most sensitive species and bluegills were the most tolerant. The total range of LC_{50} values was narrow for the seven species (13,340 to 41,760 µg/l). The three values reported for bluegills by Inglis and Davis (1972) were for tests conducted in soft, medium and hard water (50, 200, and 370 mg/l as $CaCO_3$, respectively). No significant difference was demonstrated to indicate that hardness had any effect on arsenic toxicity.

Values reported for two invertebrate and four fish species exposed to pentavalent inorganic arsenic and other arsenic compounds are listed in Table 1. All tests were static with unmeasured concentrations except for one flow-through, measured test with rainbow trout and sodium arsenate. Values reported for Daphnia magna and rainbow trout exposed to sodium arsenate (+5) are comparable to those for exposures with these species and sodium arsenite (+3). Although this data base is limited, the two valence states appear to be similarly toxic. The extremely high values reported for crayfish, channel catfish, and smallmouth bass exposed to monosodium methanearsonate indicate that organic arsenic may be much less toxic than both trivalent and pentavalent inorganic arsenic. The 96-hour LC_{50} value of 82,400 μg/l shown for fathead minnows and arsenic trisulfide (Table 6) was approximately 5 times higher than the value for this species exposed to sodium arsenite (Table 1). This is probably because arsenic trisulfide is less soluble than sodium arsenite.

Based on the above data base, the Freshwater Final Acute Value for trivalent inorganic arsenic, based on calculations described in the Guidelines, is 440 μg/l (Table 3).

Acute toxicity data representative of trivalent inorganic arsenic and saltwater aquatic life are limited to two fish and three invertebrate species (Table 1). Nelson, et al. (1976) employed a renewal test to determine the toxicity of sodium arsenite to juvenile bay scallop, and Calabrese, et al. (1973) evaluated toxicity to American oyster embryos using sodium arsenite in static tests. Toxicity tests with unmeasured concentrations defined a 96-hour LC_{50} of 3,490 µg/l for bay scallops and a 48-hour LC_{50} of 7,500 µg/l for American oyster. The lowest arsenic acute value reported (508 µg/l) was for a copepod tested in static toxicity tests with sodium arsenite.

Alderdice and Brett (1957) assessed the toxicity of arsenic trioxide to chum salmon using a renewal test with unmeasured concentration to determine the 48-hour LC_{50} of 8,330 µg/l (Table 6). The 96-hour LC_{50} values for arsenic for the fourspine stickleback and Atlantic silverside were determined to be 15,000 and 16,000 µg/l, respectively (Table 1).

Toxicity of arsenic trisulfide to juvenile white shrimp was tested by Curtis, et al. (1979). A 96-hour LC_{50} of 24,700 µg/l was determined for this less soluble form of the element in static tests (Table 6). No comparable data are available with this species for any other form of trivalent arsenic, but the highest of the five available values is 16,033 µg/l.

Chronic Toxicity

Only one chronic test was reported that could be used to calculate a chronic value for arsenic and freshwater aquatic organisms. A life-cycle test with *Daphnia magna* (U.S. EPA, 1980) (Table 2) exposed to sodium arsenite resulted in a chronic value of 912 µg/l based on chronic limits of 633 and 1,315 µg/l. A life-cycle test with the same species (Table 6) exposed to sodium arsenate could not be used in the calculation of a chronic value because the test concentrations were not measured as specified in the Guidelines. However, the upper and lower chronic limits in this test, based on reproduction growth, and enzyme inhibition were nearly identical (520 to 1,400 µg/l) to that reported above for *Daphnia magna*. Both tests were conducted in Lake Superior water. The similar toxicity reported in these tests using trivalent and pentavalent inorganic arsenic suggests that these forms are similarly toxic as was noted previously with acute tests.

Because less than the required number of chronic tests were reported for arsenic according to the Guidelines, a Freshwater Final Chronic Value cannot be calculated.

No data are available on the chronic toxicity of arsenic to saltwater fish or invertebrate species.

Plant Effects

The effect of trivalent inorganic arsenic on three species of algae and one submerged plant are reported in Table 4. All tests were conducted with sodium arsenite (Cowell, 1965). The sensitivity of aquatic plants is comparable to that for sensitive invertebrate species exposed in acute tests.

No data are available for saltwater algae or vascular plants.

Residues

Bioconcentration factors for freshwater organisms and arsenic are shown in Table 5. Values were obtained for four invertebrate and two fish species for trivalent inorganic arsenic compounds. Six species were tested with other arsenic compounds. Numerous other studies reporting bioconcentration factors for aquatic organisms were not used since they did not meet the requirements described in the Guidelines.

In the study by Spehar, et al. (1980), arsenic was tested to compare the bioconcentration of four arsenic compounds after approximately 28 days of exposure. Results indicated that *Daphnia magna* and one snail, *Helisoma campanulata*, had the highest residues when exposed to trivalent inorganic arsenic. Another snail species, *Stagnicola emarginata*, and stoneflies exposed to trivalent inorganic arsenic had values similar to organisms exposed to the other compounds. Bioconcentration factors for rainbow trout and scuds were reported as zero because residues in exposed animals were not different from those in the controls. No value was reported for scuds and trivalent inorganic arsenic (arsenic trioxide) because the concentration tested was lethal after 2 weeks of exposure.

A bioconcentration factor of 4 was obtained for bluegills and arsenic trioxide in another study (U.S. EPA, 1978). The half-life in bluegill tissue was one day. The low bioconcentration and short half-life of arsenic in fish tissue suggest that no residue problem will occur at concentrations that are not directly toxic.

A bioconcentration factor of 350 was obtained for the oyster, *Crassostrea virginica*, after 112 days of exposure (U.S. EPA., 1980b)

No Residue Limited Toxicant Concentration (RLTC) for arsenic could be determined since no maximum permissible tissue concentration for arsenic is available.

Miscellaneous

Data on other toxicological effects show that there is a wide range of sensitivity of freshwater invertebrate and fish species to arsenic (Table 6). Comparison of these data for fish with the fish acute values (Table 1) indicates that in almost all cases, arsenic toxicity was increased with increased duration of exposure. One value for bluegills (Hughes and Davis, 1967) was an exception resulting in a 48-hour LC_{50} of 290 µg/l. This value was included in the document because it was verified by the author and because there was no reason to exclude the data. A specialized pelletized form of sodium arsenite was used which may have accounted for its high toxicity. The invertebrate data were too variable to indicate a trend in toxicity in regard to duration of exposure.

Not enough data were obtained to compare the toxicity of trivalent inorganic arsenic to that of other arsenic compounds. As with the acute tests, the trivalent form, particularly sodium arsenite, was the compound most extensively tested.

Temperature was the only variable tested to determine effects of environmental factors on arsenic toxicity to freshwater organisms. Sorenson (1976c) found that increased water temperature decreased the median lethal time of green sunfish after exposure to two concentrations of sodium arsenate (Table 6).

Generally, the lowest freshwater toxicity values for arsenic were obtained in exposures with early life stages of fish. Values for early life stage exposures with rainbow trout and goldfish embryos and larvae were several times lower than those for older juvenile stages of these species. Data for bluegills showed that fingerling stages exposed to sodium arsenite were more sensitive than juveniles and adults of this species. Acute data (Table 1) also showed that channel catfish fingerlings were slightly more sensitive than juvenile stages exposed to sodium arsenite. The lowest value obtained for all of the arsenic data was for an early life stage exposure with the toad which resulted in a 7-day LC_{50} of 40 µg/l (Birge, 1979).

Values obtained for early life stages of fish species were lower than those obtained for the most sensitive invertebrate species (Table 1) and were below the limits obtained for a life cycle test with Daphnia magna (Table 2).

Bryan (1976) exposed the saltwater polychaete worm, Nereis diversicolor, to sodium arsenite and estimated the 192-hour LC_{50} to be greater than 14,500 µg/l (Table 6).

Sodium arsenite caused other effects which include depressed oxygen consumption rate and behavioral changes in mud snails exposed to sodium arsenite at concentrations of arsenic greater than 2,000 µg/l for 72 hours (MacInnes and Thurberg, 1973) and arrested development of red alga sporelings following exposure to 577 µg/l for 18 hours and a post-exposure period of seven days (Boney, et al. 1959).

Holland, et al. (1960) determined tolerance levels of pink salmon to arsenic trioxide and determined a 96-hour LC_{100} of 12,307 µg/l; a 7-day LC_{100} of 7,195 µg/l; and a 10-day LC_{54} of 3,787 µg/l.

The bioconcentration factor of 15, calculated from Nelson, et al. (1976) for the bay scallop after only a 4-day exposure, has been included for informational value.

Summary

The chemistry of arsenic in water is complex and the form present in solution is dependent on such environmental conditions as Eh, pH, organic content, presence of suspended solids, and sediment characteristics. Based on freshwater data, trivalent inorganic arsenic (with the exception of arsenic trisulfide) and the pentavalent form appear to be similarly toxic to aquatic organisms. Organic arsenic compounds and arsenic trisulfide were much less toxic but additional data are needed to adequately determined their effect on aquatic life.

Acute data for 14 freshwater species show that differences in toxicity were not related to the type of exposure (i.e., static or flow-through tests). Acute values for trivalent inorganic arsenic ranged from 812 to 41,760 µg/l. A life cycle test was conducted with Daphnia magna which gave a chronic value of 912 µg/l. No chronic tests with freshwater fish species were reported.

The freshwater residue data indicate that arsenic is not bioconcentrated to a high degree and that lower forms of aquatic life may accumulate higher arsenic residues than fishes. Arsenic accumulation in freshwater aquatic organisms does not appear to be greatly affected by the form of arsenic present, although the highest residues were seen in exposures with the trivalent inorganic form. The highest arsenic bioconcentration factor was found in one test with a saltwater bivalve mollusc which indicates that these organisms may accumulate more arsenic than freshwater organisms.

The freshwater plant data suggest that concentrations of arsenic which are toxic to aquatic plants are also acutely toxic to aquatic invertebrate species.

The other toxicological data revealed a wide range of toxicity based on tests with 16 freshwater species and several endpoints of effect. Comparisons of these data with acute tests showed that arsenic toxicity was increased with increased exposure time. Higher temperatures also appeared to increase arsenic toxicity whereas water hardness had no significant effect. Effects of other parameters such as pH, suspended solids, and organic content in the water were not found in the literature.

Early life stages of freshwater aquatic organisms appear to be the most sensitive indicator of arsenic toxicity and should be used as the basis for formulating criteria for arsenic in water. The lowest effect concentration for arsenic and freshwater organisms is 40 µg/l.

Trivalent inorganic arsenic acute values for saltwater fish species were 16,000 µg/l for Atlantic silverside and 15,000 µg/l for the fourspine stickleback; and, among three invertebrate species, acute values ranged from 508 µg/l for a copepod and 7,500 µg/l for the American oyster. No chronic, plant, or equilibrium residue data are available for any saltwater species and arsenic.

CRITERIA

For freshwater aquatic life the concentration of total recoverable trivalent inorganic arsenic should not exceed 440 µg/l at any time. Short-term effects on embryos and larvae of aquatic vertebrate species have been shown to occur at concentrations as low as 40 µg/l

The available data for total recoverable trivalent inorganic arsenic indicate that acute toxicity to saltwater aquatic life occurs at concentrations as low as 508 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of trivalent inorganic arsenic to sensitive saltwater aquatic life.

Table 1. Acute values for arsenic

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
		FRESHWATER SPECIES			
		Trivalent Inorganic Arsenic			
Cladoceran, *Daphnia magna*	S, U	Sodium arsenite	5,278	5,278	Anderson, 1946
Cladoceran, *Daphnia pulex*	S, U	Sodium arsenite	1,044	-	Sanders & Cope, 1966
Cladoceran, *Daphnia pulex*	S, U	Sodium arsenite	1,740	1,348	FPRL, 1980
Cladoceran, *Simocephalus serrulatus*	S, U	Sodium arsenite	812	812	Sanders & Cope, 1966
Scud, *Gammarus pseudolimnaeus*	FT, M	Sodium arsenite	879	879	U.S. EPA, 1980a
Stonefly, *Pteronarcys californica*	S, U	Sodium arsenite	22,040	-	Sanders & Cope, 1968
Stonefly, *Pteronarcys californica*	S, U	Sodium arsenite	22,040	22,040	FPRL, 1980
Rainbow trout, *Salmo gairdneri*	S, U	Sodium arsenite	13,340	13,340	FPRL, 1980
Brook trout, *Salvelinus fontinalis*	FT, M	Sodium arsenite	14,964	14,964	Cardwell, et al. 1976
Goldfish (juvenile), *Carassius auratus*	FT, M	Sodium arsenite	26,042	26,042	Cardwell, et al. 1976
Fathead minnow (juvenile), *Pimephales promelas*	FT, M	Sodium arsenite	15,660	15,660	Cardwell, et al. 1976
Channel catfish (juvenile), *Ictalurus punctatus*	FT, M	Sodium arsenite	18,096	-	Cardwell, et al. 1976

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Channel catfish (fingerling), Ictalurus punctatus	S, U	Sodium arsenite	15,022	18,096	Clemens & Sneed, 1959
Flagfish (fry), Jordanella floridae	FT, M	Sodium arsenite	28,130	28,130	Cardwell, et al. 1976
Bluegill (juvenile), Lepomis macrochirus	FT, M	Sodium arsenite	41,760	-	Cardwell, et al. 1976
Bluegill, Lepomis macrochirus	S, U	Sodium arsenite	15,370	-	Inglis & Davis, 1972
Bluegill, Lepomis macrochirus	S, U	Sodium arsenite	16,240	-	Inglis & Davis, 1972
Bluegill, Lepomis macrochirus	S, U	Sodium arsenite	15,486	-	Inglis & Davis, 1972
Bluegill, Lepomis macrochirus	S, U	Sodium arsenite	17,400	41,760	FPRL, 1980
		Pentavalent Inorganic Arsenic			
Cladoceran, Daphnia magna	S, U	Sodium arsenate	7,400	7,400	Biesinger & Christensen, 1972
Rainbow trout (juvenile), Salmo gairdneri	FT, M	Sodium arsenate	10,800	10,800	Hale, 1977
		Other Arsenic Compounds			
Crayfish, Procambarus sp.	S, U	Monosodium methanearsonate	506,000	506,000	Anderson, et al. 1975
Channel catfish, Ictalurus punctatus	S, U	Monosodium methanearsonate	1,403,000	1,403,000	Anderson, et al. 1975

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Smallmouth bass (fingerling), *Micropterus dolomieu*	S, U	Monosodium methanearsonate	414,000	414,000	Anderson, et al. 1975
		SALTWATER SPECIES			
		Trivalent Inorganic Arsenic			
Bay scallop (juvenile), *Argopecten irradians*	R, U	Sodium arsenite	3,490	3,490	Nelson, et al. 1976
American oyster, *Crassostrea virginica*	S, U	Sodium arsenite	7,500	7,500	Calabrese, et al. 1973
Copepod, *Acartia clausi*	S, U	Sodium arsenite	508	508	U.S. EPA, 1980b
Fourspine stickleback, *Apeltes quadracus*	S, U	Sodium arsenite	14,953	15,000	U.S. EPA, 1980b
Atlantic silverside (juvenile), *Menidia menidia*	S, U	Sodium arsenite	16,033	16,000	U.S. EPA, 1980b

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* S = static, R = renewal, FT = flow-through, U = unmeasured, M = measured

**Results are expressed as arsenic, not as the compound.

Table 2. Chronic values for arsenic

Species	Test*	Chemical	Limits (µg/l)**	Chronic Value (µg/l)**	Reference
FRESHWATER SPECIES					
Trivalent Inorganic Arsenic					
Cladoceran, *Daphnia magna*	LC	Sodium arsenite	633-1,315	912	U.S. EPA, 1980a

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* LC = life cycle or partial life cycle

**Results are expressed as arsenic, not as the compound

Acute-Chronic Ratio

Species	Chemical	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Trivalent Inorganic Arsenic				
Cladoceran, *Daphnia magna*	Sodium arsenite	5,278	912	5.8

Table 3. Species mean acute values and acute-chronic ratios for arsenic

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
	Trivalent Inorganic Arsenic		
12	Bluegill, *Lepomis macrochirus*	41,760	-
11	Flagfish, *Jordanella floridae*	28,130	-
10	Goldfish, *Carassius auratus*	26,042	-
9	Stonefly, *Pteronarcys californica*	22,040	-
8	Channel catfish, *Ictalurus punctatus*	18,096	-
7	Fathead minnow, *Pimephales promelas*	15,660	-
6	Brook trout, *Salvelinus fontinalis*	14,964	-
5	Rainbow trout, *Salmo gairdneri*	13,340	-
4	Cladoceran, *Daphnia magna*	5,278	5.8
3	Cladoceran, *Daphnia pulex*	1,348	-
2	Scud, *Gammarus pseudolimnaeus*	879	-
1	Cladoceran, *Simocephalus serrulatus*	812	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	SALTWATER SPECIES		
	Trivalent Inorganic Arsenic		
5	Atlantic silverside, *Menidia menidia*	16,033	-
4	Fourspine stickleback, *Apeltes quadracus*	14,953	-
3	American oyster, *Crassostrea virginica*	7,500	-
2	Bay scallop, *Argopectin irradians*	3,490	-
1	Copepod, *Acartia clausi*	508	-

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* Ranked from least sensitive to most sensitive based on species mean acute value.

Freshwater Final Acute Value for trivalent inorganic arsenic = 440 µg/l

Table 4. Plant values for arsenic

Species	Chemical	Effect	Result (µg/l)*	Reference
		FRESHWATER SPECIES		
		Trivalent Inorganic Arsenic		
Alga, *Cladophora* sp.	Sodium arsenite	100% kill in 2 wks	2,320	Cowell, 1965
Alga, *Spirogyra* sp.	Sodium arsenite	100% kill in 2 wks	2,320	Cowell, 1965
Alga, *Zygnema* sp.	Sodium arsenite	100% kill in 2 wks	2,320	Cowell, 1965
Submerged plant, *Potamogeton* sp.	Sodium arsenite	95% kill in 1 mo	2,320	Cowell, 1965

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* Results are expressed as arsenic, not as the compound.

Table 5. Residues for arsenic

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		FRESHWATER SPECIES			
		Trivalent Inorganic Arsenic			
Cladoceran, *Daphnia magna*	Whole body	Arsenic trioxide	10	21	Spehar, et al. 1980
Snail, *Helisoma campanulata*	Whole body	Arsenic trioxide	17	28	Spehar, et al. 1980
Snail, *Stagnicola emarginata*	Whole body	Arsenic trioxide	3	28	Spehar, et al. 1980
Stonefly, *Pteronarcys dorsata*	Whole body	Arsenic trioxide	9	28	Spehar, et al. 1980
Rainbow trout, *Salmo gairdneri*	Whole body	Arsenic trioxide	0	28	Spehar, et al. 1980
Bluegill, *Lepomis macrochirus*	Whole body	Arsenic trioxide	4	28	U.S. EPA, 1978
		Pentavalent Inorganic Arsenic			
Cladoceran, *Daphnia magna*	Whole body	Arsenic pentoxide	4	21	Spehar, et al. 1980
Scud, *Gammarus pseudolimnaeus*	Whole body	Arsenic pentoxide	0	28	Spehar, et al. 1980
Snail, *Helisoma campanulata*	Whole body	Arsenic pentoxide	6	28	Spehar, eta l. 1980
Snail, *Stagnicola emarginata*	Whole body	Arsenic pentoxide	3	28	Spehar, et al. 1980
Stonefly, *Pteronarcys dorsata*	Whole body	Arsenic pentoxide	7	28	Spehar, et al. 1980
Rainbow trout, *Salmo gairdneri*	Whole body	Arsenic pentoxide	0	28	Spehar, et al. 1980

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		Other Arsenic Compounds			
Cladoceran, *Daphnia magna*	Whole body	Disodium methyl arsenate	4	21	Spehar, et al. 1980
Cladoceran, *Daphnia magna*	Whole body	Sodium dimethyl arsenate	4	21	Spehar, et al. 1980
Scud, *Gammarus pseudolimnaeus*	Whole body	Disodium methyl arsenate	0	28	Spehar, et al. 1980
Scud, *Gammarus pseudolimnaeus*	Whole body	Sodium dimethyl arsenate	0	28	Spehar, et al. 1980
Snail, *Helisoma campanulata*	Whole body	Disodium methyl arsenate	4	28	Spehar, et al. 1980
Snail, *Helisoma campanulata*	Whole body	Sodium dimethyl arsenate	5	28	Spehar, et al. 1980
Snail, *Stagnicola emarginata*	Whole body	Disodium methyl arsenate	3	28	Spehar, et al. 1980
Snail, *Stagnicola emarginata*	Whole body	Sodium dimethyl arsenate	2	28	Spehar, et al. 1980
Stonefly, *Pteronarcys dorsata*	Whole body	Disodium methyl arsenate	9	28	Spehar, et al. 1980
Stonefly, *Pteronarcys dorsata*	Whole body	Sodium dimethyl arsenate	7	28	Spehar, et al. 1980
Rainbow trout, *Salmo gairdneri*	Whole body	Disodium methyl arsenate	0	28	Spehar, et al. 1980
Rainbow trout, *Salmo gairdneri*	Whole body	Sodium dimethyl arsenate	0	28	Spehar, et al. 1980

Table 5. (Continued)

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		SALTWATER SPECIES			
		Trivalent Inorganic Arsenic			
Oyster, *Crassostrea virginica*	Soft parts	Sodium arsenite	350	112	U.S. EPA, 1980b

Table 6. Other data for arsenic

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
FRESHWATER SPECIES					
Trivalent Inorganic Arsenic					
Cladoceran, (not specified)	Sodium arsenite	1 wk	Significant population reduction	2,320	Cowell, 1965
Cladoceran, Daphnia magna	Sodium arsenite	26 hrs	IC50 (median immobilization)	3,770	Crosby & Tucker, 1966
Cladoceran, (not specified)	Sodium arsenite	16 wks	Reduced population (one treatment)	690	Gilderhus, 1966
Copepod (adult), (not specified)	Sodium arsenite	16 wks	Reduced population (weekly treatments)	690**	Gilderhus, 1966
Copepod, (not specified)	Sodium arsenite	1 wk	Significant population reduction	2,320	Cowell, 1965
Rotifer, (not specified)	Sodium arsenite	1 wk	Significant population reduction	2,320	Cowell, 1965
Rotifer, (not specified)	Sodium arsenite	16 wks	Reduced population (monthly treatments)	690***	Gilderhus, 1966
Amphipod, Hyalella knickerbockeri	Arsenic trioxide	5 days	70% mortality	4,469	Surber & Meehean, 1931
Amphipod, Gammarus pseudolimnaeus	Arsenic trioxide	7 days	80% mortality	961	Spehar, et al. 1980
Mayfly (nymph), Caenis diminuta	Arsenic trioxide	5 days	25% mortality	2,234	Surber & Meehean, 1931
Mayfly (nymph), Caenis diminuta	Arsenic trioxide	5 days	62% mortality	5,958	Surber & Meehean, 1931
Mayfly, Callibaetis sp.	Arsenic trioxide	5 days	94% mortality	4,469	Surber & Meehean, 1931
Toad (embryo-larval), Gastrophryne carolinensis	Sodium arsenite	7 days	LC50	40	Birge, 1979

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
Rainbow trout (embryo-larval), Salmo gairdneri	Sodium arsenite	28 days	LC50	540	Birge, 1979
Rainbow trout (juvenile), Salmo gairdneri	Arsenic trioxide	21 days	Decrease in fat weight gain	1,000	Speyer, 1974; Speyer & Leduc, 1975
Brook trout, Salvelinus fontinalis	Sodium arsenite	262 hrs	LC50	10,440	Cardwell, et al. 1976
Goldfish (juvenile), Carassius auratus	Sodium arsenite	336 hrs	LC50	18,618	Cardwell, et al. 1976
Goldfish (embryo-larval), Carassius auratus	Sodium arsenite	7 days	LC50	490	Birge, 1979
Spottail shiner, Notropis hudsonius	Sodium arsenite	72 hrs	LC50	27,000	Boschetti & McLoughlin, 1957
Fathead minnow (juvenile), Pimephales promelas	Sodium arsenite	336 hrs	LC50	10,556	Cardwell, et al. 1976
Fathead minnow, Pimephales promelas	Arsenic trisulfide	96 hrs	LC50	82,400	Curtis, et al. 1979
Bluegill (juvenile), Lepomis macrochirus	Sodium arsenite	16 wks	Reduced survival (one treatment)	690	Gilderhus, 1966
Bluegill (adult), Lepomis macrochirus	Sodium arsenite	16 wks	Histopathological alterations (weekly treatments)	690**	Gilderhus, 1966
Bluegill (juveniles), Lepomis macrochirus	Sodium arsenite	336 hrs	LC50	18,328	Cardwell, et al. 1976
Bluegill (fingerling), Lepomis macrochirus	Sodium arsenite (pelletized)	48 hrs	LC50	290	Hughes & Davis, 1967

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
		Pentavalent Inorganic Arsenic			
Cladoceran, *Daphnia magna*	Sodium arsenate	3 wks	LC50	2,850	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	Sodium arsenate	3 wks	Chronic limits	520-1,400	Biesinger & Christensen, 1972
Green sunfish (juvenile), *Lepomis cyanellus*	Sodium arsenate	39 hrs	LT50	40,000	Sorenson, 1976a
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	2 wks	Ultrastructural changes in liver	31,700	Sorenson, 1976b
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	678 hrs	LT50 at 10 C	60,000	Sorenson, 1976c
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	210 hrs	LT50 at 20 C	60,000	Sorenson, 1976c
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	124 hrs	LT50 at 30 C	60,000	Sorenson, 1976c
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	527 hrs	LT50 at 20 C	30,000	Sorenson, 1976c
Green sunfish, *Lepomis cyanellus*	Sodium arsenate	209 hrs	LT50 at 30 C	30,000	Sorenson, 1976c
		SALTWATER SPECIES			
		Trivalent Inorganic Arsenic			
Red alga, *Plumaria elegans*	Sodium arsenite	18 hrs	7 day post exposure - arrested development of sporelings	577	Boney, et al. 1959
Polychaete worm, *Nereis diversicolor*	Sodium arsenite	192 hrs	LC50	>14,500	Bryan, 1976

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
Mud snail, *Nassarius obsoletus*	Sodium arsenite	72 hrs	O_2 consumption rate depressed and abnormal behavior	>2,000	MacInnes & Thurberg 1973
Bay scallop (juvenile), *Argopectin irradians*	Sodium arsenite	4 days	Bioconcentration factor = 15	-	Nelson, et al. 1976
White shrimp (juvenile), *Penaeus setiferus*	Arsenic trisulfide	96 hrs	LC50	24,700	Curtis, et al. 1979
Pink salmon, *Oncorhynchus gorbuscha*	Arsenic trioxide	96 hrs	LC100	12,307	Holland, et al. 1960
Pink salmon, *Oncorhynchus gorbuscha*	Arsenic trioxide	7 days	LC100	7,195	Holland, et al. 1960
Pink salmon, *Oncorhynchus gorbuscha*	Arsenic trioxide	10 days	LC54	3,787	Holland, et al. 1960
Chum salmon, *Oncorhynchus keta*	Arsenic trioxide	48 hrs	LC50	8,330	Alderdice & Brett, 1957

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* Results are expressed as arsenic, not as the compound.

** Measured concentration after 16 weeks was 9,040 µg/l

***Measured concentration after 16 weeks was 2,280 µg/l

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

In a U.S. Environmental Protection Agency national study of residential tap water, 66.8 percent of the one-time grab samples collected from 3,834 residences had arsenic levels greater than 0.1 µg/l. The average, minimum, and maximum arsenic levels of the samples were 2.37, 0.50, and 213.6 µg/l, respectively (Greathouse and Craun, 1978). In 1975 it was reported that 5 out of 566 samples collected from Interstate Carrier Water Supplies exceeded 10 µg/l and that the maximum level was 60 µg/l (U.S. EPA, 1975). Well water samples collected during 1976 at 59 residences in a Fairbanks, Alaska surburban community had a mean arsenic content of 224 µg/l with a range from 1.0 to 2,450 µg/l (U.S. Public Health Service, 1977). Valentine, et al. (1979) reported that arsenic levels in the water supply from five communities (Fairfax and Edison in Bakersfield, California; and Virginia Foothills, Hidden Valley, and Fallon in Nevada) to be 6, 393, 51, 123, and 98 µg/l, respectively.

There have been a number of other reports of isolated instances of higher than usual concentrations of arsenic in well waters. Goldsmith, et al. (1972) reported on a study, in Lassen County, California, of the health effects associated with drinking well waters with arsenic levels ranging from 100 µg/l or less to 1,400 µg/l. In Perham, Minnesota, a newly bored well was associated with illness in 13 people whose hair samples contained arsenic at 37-1,680 µg/g. The well water serving these patients contained arsenic from 11,800 to 21,000 µg/l; this was later determined to come from ground contamination by residual arsenical grasshopper bait (Feinglass, 1973).

Forty-five out of 558 water samples collected from Lane County, Oregon had arsenic values greater than 50 µg/l. The mean, maximum, and minimum values detected were 9.6, 2,150, and 0 µg/l, respectively (Morton, et al. 1976).

Much information has been collected concerning the levels of arsenic in fresh surface waters (Table 1). Arsenic occurrence is very widespread and even occurs in some rain water. Most of the high values reported in rivers and lakes are probably due to industrial contamination [National Academy of Sciences (NAS), 1977a]. Angino, et al. (1970) have shown that household detergents (mostly of the high-phosphate type) widely used in the United States contained arsenic at 1-73 µg/g; their use probably contributes significant amounts of arsenic to surface sources. Sollins (1970), however, felt that, after dilution during use, the concentration would be well below the recommended maximum and constitute no particular hazard. It has been generally assumed that surface waters, like the ocean, are "self-purifying" with respect to arsenic - i.e., arsenic is removed from solution by deposition with sediments; but quantitative studies are lacking. Sediments are always higher in arsenic than the waters with which they are associated (NAS, 1977a).

Ingestion from Food

A 1966 food survey found arsenic in 3.2 percent of the samples at a range of 0.10 to 4.7 µg/g (Cummings, 1966). In a 1967 market-basket survey, arsenic was present in 10 percent of the composite samples (Duggan and Lipscomb, 1969). In 1968, arsenic occurred in 18 percent of the samples. Whether arsenic occurred naturally or as a result of man's activities was not known.

Schroeder and Balassa (1966) sampled foods and beverages from American chain stores (Table 2). Fish and seafoods contained the most arsenic

TABLE 1

Arsenic in Fresh Surface Waters

Water	Arsenic Concentration µg/l	Reference
United States		
Lakes:		
New York, Chautauqua	3.5-35.6	Lis and Hopke, 1973
Michigan	0.5-2.4	Seydel, 1972
Superior	0.1-1.6	Seydel, 1972
Wisconsin	4.0-117	Chamberlain and Shapiro, 1969
California, Searles	198,000-243,000	White, et al. 1963
	0.0-110[a]	Livingston, 1963
	0.0-2,000[b]	Livingston, 1963
Florida, Echols	3.58	Braman and Foreback, 1973
Florida, Magdelene	1.75	Braman and Foreback, 1973
Rivers:		
Hillsborough	0.25	Braman and Foreback, 1973
Withlacoochee	0.42	Braman and Foreback, 1973
Fox (polluted watershed)	100-6,000	Brown, et al. 1973
Yellowstone	4.5	Ellis, 1934
Narrow	0.90	Ray and Johnson, 1972
Providence	0.75-0.90	Ray and Johnson, 1972
Seekoink	2.48-3.45	Ray and Johnson, 1972
Sugar Creek (contaminated)	10-1,100	Durum et al. 1971: Wilder, 1972
Columbia	1.6	Onishi, 1969
Schuylkill	30-180	Kopp, 1967
Canals:		
Florida	10-20	Grantham and Sherwood, 1968

TABLE 1 (cont.)

Water	Arsenic Concentration µg/l	Reference
Puget Sound	1.5-1,200	Crecelius, et al. 1975; Crecelius and Carpenter, 1974
Rainwater:		
Rhode Island	0.82	Ray and Johnson 1972
Washington, Seattle	17	Crecelius, et al. 1975
Chile	800	Borgono and Greiber, 1972
Formosa, well water	800	Fan and Yang, 1969

[a] Dissolved solids, <2,000 mg/l

[b] Dissolved solids, >2,000 mg/l

TABLE 2

Arsenic in Foods*
(wet weight)

Food Sample	Arsenic Concentration (μg/l)	Micrograms of Arsenic per 100 cal[a]
Fish and sea food		
Haddock	2.17	305
Kingfish	8.86	886
Oysters, fresh	2.9	580
Oysters, frozen	2.7	540
Scallops, fresh	1.67	160
Shrimp, fresh frozen	1.50	132
Shrimp shells	15.3	—
Clams, fresh frozen	2.52	525
Conch, fresh	3.1	311
Conch, dried, whole	5.63	311
Meats		
Beef, stewing	1.3	58
Pork loin	0.06	21
Pork liver, No. 1	1.07	75
Pork liver, No. 2	1.4	98
Pork kidney	0.0	0
Lamb chop	0.35	19
Chicken breast	0.0	0
Gelatin	0.19	6
Egg lecithin	0.0	0
Vegetables and grains		
Wheats, whole	0.17	5
Rye, seed	0.16	5
Corn	0.11	3
Corn meal	0.78	22
Corn oil	0.0	0
Corn oil lecithin	0.0	0
Rice, Madagascar	0.48	13
Rice, U.S.	0.13	3
Puffed rice	1.6	46
Kelloggs' Special K^R	0.66	19
Cottonseed oil	0.0	0
Beets	0.0	0

TABLE 2 (cont.)

Food Sample	Arsenic Concentration (µg/l)	Micrograms of Arsenic per 100 cal[a]
Vegetables and grains (cont'd)		
Beet greens	0.24	240
Swiss chard	0.56	215
Rhubarb	0.48	800
Red pepper	0.06	--
Garlic, fresh	0.24	--
Cherry tomatoes	0.37	264
Yellowpear tomatoes	0.10	70
Turnip	0.0	0
Mushrooms	2.9	414
Soy lecithin	0.0	0
Vegetables, St. Thomas, V.I.		
Carrots	0.0	0
Peas, dried	0.09	3
Peas, fresh	0.0	0
Tomatoes, fresh	0.0	0
Egg plant	0.82	546
Ginger	0.0	
Fruits		
Apple	0.0	0
Orange	0.0	0
Pear	0.0	0
Grapes, wild	0.17	34
Miscellaneous		
Cocoa, Hershey's®	0.59	13
Coffee	0.0	0
Tea	0.89	-
Salt, table	2.71	-
Salt, sea	2.83	-
Sugar, lump	0.10	3
Sugar, granulated	0.0	0
Milk, evaporated	0.17	11
Milk, dry skimmed	0.0	0
Butter, unsalted	0.23	3

*Source: Schroeder and Balassa, 1966

[a] Calorie values from McCance and Widdowson, 1947

and fruits contained the least. Generally, the only foods which are high in arsenic are seafoods. Chapman (1926) found that mussels, oysters, and scallops contained very high levels of arsenic (means of up to 80 µg/g). In comparison, mixed freshwater fish contained a mean of 0.65 µg/g arsenic. Zook, et al. (1976) reported that in a survey of selected seafoods for metal content, the overall arsenic mean content was 2.6 µg/g. The lowest mean arsenic value was found in wild catfish - 0.1 µg/g. Thus, arsenic appears to be present in small amounts in nearly all foods, with marine invertebrates containing the highest arsenic levels (Table 3).

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of arsenic which might be ingested from the consumption of fish and shellfish. Residue data for a variety of inorganic compounds indicate that bioconcentration factors for the edible portion of most aquatic animals are similar, except that for some compounds bivalve molluscs (clams, oysters, scallops, and mussels) should be considered a separate group. An analysis (U.S. EPA, 1980a) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). The per capita consumption of bivalve molluscs is 0.8 g/day and that of all other freshwater and estuarine fish and shellfish is 5.7 g/day.

Spehar, et al. (1980) obtained bioconcentration factors of zero for four different arsenic compounds in rainbow trout, but a BCF of 4 was obtained with the bluegill (U.S. EPA, 1978). Thus, the BCF for arsenic is probably about 1.0 for many aquatic animals a BCF of 350 was obtained for sodium arsenite with in oysters. If the values of 350 and 1 are used with the

TABLE 3

Bioaccumulation Ratio Values for Arsenic in Aquatic Organisms[a]*

Species	Arsenic in Tissue (μg/l)	Bioaccumulation Ratio Values[b]
Haddock	2-10.8	1,000-5,400[c]
Kingfish	8.86	4,430
Crustacea and shellfish	1.5-3.1	750-1,550
	0.018-1.06	9-530
Assorted fish	0.076-2.27	38-1,135
Assorted fish	<1-6.4	<500-3,200[c]
Shrimp	3.6-48	1,836-64,100[c]
Mackerel	4.7-9.2	2,350-4,600[c]
Cod	24.3	12,150[c]
Assorted freshwater fish	0.1-0.2	10-20
	0.035-0.298	3-30[d]

*Source: Woolson, 1975 (Data collected from several sources)

[a] Concentration in tissue/concentration in water

[b] A marine concentration of 2 μg arsenic per liter is used in all calculations

[c] Dry weight basis

[d] Water concentration assumed to be 10 μg arsenic per liter

consumption data, the weighted average bioconcentration factor for arsenic and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans is calculated to be 44.

Crecelius (1977a) has analyzed 19 samples of domestic table wines for several species of arsenic; 13 varieties of white and red wines were included. The ranges of concentrations were <1-420 μg/l, <1-110 μg/l, and <1-530 μg/l for arsenite, arsenate, and total arsenic, respectively. Mean levels were 127, 32, and 153 μg/l, respectively. Clearly, the majority of the arsenic was present as arsenite. Both dimethylarsinic acid and methylarsonic were below the detection limit of 1 μg/l in these wine samples.

In 1966 Schroeder and Balassa (1966) estimated that the average daily diet contains 900 μg of arsenic. This estimate was based on the results of arsenic determinations for meats, sea food, and vegetables purchased from Vermont chain stores. Arsenic in an institutional diet was estimated to be 400 μg per day. One reason for this lower level is that the institutional diet did not contain any seafood. The World Health Organization reported that arsenic intakes vary from 7 to 60 μg per day (NAS, 1977a). Jelinek and Corneluissen (1977) reported that the Food and Drug Administration (FDA) has monitored for arsenic in its Total Diet Survey since inception of the program. The data from this program indicated that the average daily intake for arsenic trioxide has decreased from about 130 μg/day in 1968 to about 20 μg/day in 1974. It is likely that the differences among the estimates of total daily intake are partially due to variations in the species of arsenic considered.

Arsenic was known as a therapeutic agent to the ancient Greeks and Romans. The introduction of Salvarsan (arsphenamine) by Ehrlich at the turn of the century gave rise to intense activity on the part of the organic chemists, and it is estimated that more than 32,000 arsenic compounds were synthesized (NAS, 1977a).

The advent of penicillin disposed of antiluetic arsenicals, and other newer drugs have nearly eliminated the use of other organic arsenicals. In current human therapeutics, arsenicals are of importance only in the treatment of certain tropical diseases (Harvey, 1975).

Inhalation

Suta (1978) has evaluated atmospheric arsenic concentration data for 1974 in 267 locations representing a resident population of more than 58,000,000 people. The annual average concentrations for all sites ranged from below the detection limit to 83 mg/m^3. The mean of the annual average concentrations for all locations was 3 mg/m^3. The average concentration for eight locations near nonferrous smelters was 30 mg/m^3, and the average concentration for eight locations in remote rural areas was 0.4 mg/m^3, assuming a concentration of zero for samples reported as below detection limit. The lower detection limit for an individual arsenic sample is 1 mg/m^3 (Suta, 1978).

Suta (1978) has estimated air arsenic concentrations and exposed population numbers associated with major manmade sources of arsenic in the atmosphere (Table 4). He states that due to the paucity of relevant data and information, the large number of required assumptions, and the inherent inaccuracies of the modeling approach, the accuracy of these exposure estimates cannot be judged quantitatively. It should be noted that the exposure concentrations shown in the table are annual averages. Exposures for selected times may be much higher or lower than the annual averages. Population exposures for concentrations below 3 mg/m^3 are not given because they

TABLE 4

Estimates of Population Exposures to Arsenic for Selected Emission Sources*

Average Annual Concentration[a] (mg/m^3)	Emission Source					
	Copper Smelters[b]	Lead Smelters[c]	Zinc Smelters[d]	Cotton Gin[e]	Pesticide Manufacturer[f]	Glass Manufacturing[g]
3.0-5.9				5		
1.0-2.9	2,200			100		
0.60-0.99	--			200		
0.30-0.59	17,500			700		
0.10-0.29	28,000	800	22,000	2,000		150
0.060-0.099	92,000	2,600	48,000	3,000		24,000
0.030-0.059	288,000	5,100	134,000	5,900		169,000
0.010-0.029	20,000	38,000	630,000	20,000		1,253,000
0.005-0.009	146,000	46,000	1,202,000	56,000	60	3,534,000
0.003-0.004	237,000	67,000	1,642,000	135,000	800	6,059,000
					11,900	9,490,000

*Source: Suta, 1978

[a] Average omnidirectional concentrations. With the exception of cotton gin exposures, 24-hr worst-case exposures can be estimated by multiplying the annual averages of 12.5. The 24-hr worst-case exposures for cotton gins may be obtained by multiplying the concentrations by 81.

[b] Based on EPA's estimate of stack emissions. Assumes 10 percent fugitive emissions.

[c] Based on an emission of 0.5 lb of arsenic per each ton of lead produced. Fugitive emissions are estimated to be 10 percent of stack emissions.

[d] Based on an emission of 1.3 lb of arsenic per ton of zinc produced by pyrometallurgical smelters and no stack emissions at electrolytic smelters. Fugitive emissions assumed to be 10 percent of the 1.3 lb/ton stack emissions for all smelters.

[e] Annual average exposure, assuming that ginning exposures occur during 15 percent of the year and that there are no exposures during the remainder of the year.

[f] Assumes that all large plant pesticide emissions are well controlled.

[g] Assumes that 25 percent of pressed and blown glass is manufactured with arsenic and that only certain manufacturers use arsenic in all of their pressed and blown glass production.

are assumed to be equal the average urban background concentration. Population exposures are not given for concentrations below 10 mg/m^3 for some copper smelter alternative estimates, because to do so would have required extrapolation of modeling results beyond 20 km for the source. At these greater distances, the accuracy of the modeling results became increasingly uncertain.

It is quite apparent from these qualified estimates that in some areas of the country, the general population is exposed to high levels of atmospheric arsenic when compared to ambient levels in uncontaminated areas. Klemmer, et al. (1975) analyzed 61 samples of dusts collected from homes in Hawaii for arsenic content and found that the levels ranged from 33 to 1,080 µg/g. Since house dust has been implicated as a significant source of human pesticide burden, it may also be a significant source of arsenic exposure in some homes.

Dermal

No information was found concerning the levels and/or duration of dermal exposure to arsenic. Since arsenic compounds are used in insecticides, herbicides, fungicides, algicides, sheepdips, wood preservatives, and dyestuffs and for the eradication of tapeworm in sheep and cattle (NAS, 1977a), it seems likely that the dermal route may be a source of arsenic exposure for some segments of the population.

PHARMACOKINETICS

Adequate understanding of arsenic toxicology is heavily dependent upon clear delineation of differences between various arsenic forms or compounds, e.g., organic versus inorganic arsenic compounds or trivalent versus pentavalent inorganic arsenic species, in terms of various pharmacokinetic aspects, e.g., adsorption, metabolism (especially *in vivo* biotransformations), distribution, and excretion. Important new information regarding differential characteristics of various arsenic forms in regard to such aspects has emerged in the scientific literature during the past 5 years, but has only recently begun to be critically evaluated in regard to its full meaning and implications. In addition, newly emerging evidence has recently been reported suggesting a possible essential role for arsenic in some mammalian species, carrying with it potential implications for analyses of arsenic toxicology. A thorough critical assessment of literature bearing on the above issues appears in the recently prepared EPA Health Assessment Document for Arsenic (U.S. EPA, 1980b).

Absorption

The major routes of arsenic exposure of significance for general public health are inhalation and ingestion, either via direct intake of food and water or secondary to the inhalation of arsenic in a form and size whereby it undergoes retrocilliary movement and is eventually swallowed. Inhalation is probably of more significance in occupational settings, while oral intake is a more widespread exposure route for the population at large. Percutaneous absorption of arsenic, while poorly studied, can occur in man, based on isolated reports, but appears to be a relatively minor route of exposure except under certain occupational exposure conditions.

Confusing the picture of arsenical absorption is the importance of the chemical form of the arsenical. In some studies, this has been known with more certainty than in other studies and it is difficult at times, to discern clearly relative uptake or absorption characteristics for various arsenic forms under different exposure conditions.

The extent of respiratory absorption of arsenic adsorption depends on chemical species of arsenic and the particulate size, assuming that the airborne arsenic compound is in the form of an aerosol. Smaller-sized particles (<1 μm diameter) are deposited deeper in the respiratory tract with greater subsequent absorption likely via the alveolar parenchyma than for larger-sized particles. Larger particles tend to be deposited mainly in the upper portion of the respiratory tract, undergo retrociliary movement, and ultimately are swallowed, with arsenic absorption then determined by the characteristics of gastrointestinal uptake. Precise relative rates of uptake and absorption of airborne arsenic compounds, therefore, depend upon the size of arsenic-associated particles generated from particular emission sources. In the case of emissions from high-temperature combustion sources, such as smelters and coal-fired power plants, emissions of arsenic and other toxic trace metals were found by Natusch, et al. (1974) to be mainly in the highly respirable size range of <1-2 μm.

Several studies of the respiratory deposition and absorption of arsenic by human subjects have been reported. Holland and co-workers (1959), using a group of hospital patients (lung cancer) to assess the deposition and absorption of inhaled arsenic from arsenite-containing cigarettes labeled with arsenic-74 and arsenite-containing aerosols, observed that 75 to 85 percent of the deposited arsenic was absorbed from the lungs within 4 days. In another study (Pinto, et al. 1976) on a group of workers exposed to airborne arsenic in a copper smelter, average urinary arsenic excretion values ranging from 38 to 539 μg/l were found to be associated with average air levels of arsenic ranging from 3 to 295 $\mu g/m^3$ (overall 53 μg As/m^3). Urinary arsenic was highly correlated with workplace air exposure (0.53, $p<0.01$). In a later study of copper smelter workers, Smith, et al. (1977) found that variations in concentrations of all arsenic forms isolated in urine, namely trivalent, pentavalent, methyl-, and dimethylarsenic, were directly correlated with levels of airborne exposure.

Animal data have also been reported on arsenic absorption via the respiratory tract. Bencko and Symon (1970) observed that hairless mice breathing a solid aerosol of fly ash containig 180 µg As/m^3 for several weeks had increases in tissue arsenic values. Since the particle size was determined to be only less than 10 µm, part of this intake may have occurred via the GI tract. Increases in tissue arsenic in two exposure groups also occurred when rats were exposed to arsenic trioxide (condensation aerosols: 1.0, 3.7, and 46 µg/m^3) for 90 days (Rozenshtein, 1970). Similarly, relatively rapid absorption of pentavalent arsenic was noted by Dutkiewicz (1977) when rats were exposed intratracheally (arsenate solution labeled with arsenic-74; 0.1 and 4.0 mg/kg). Arsenic tissue distribution dynamics were similar for the intratracheal and a companion intravenous exposure study, indicating that the rate of arsenic uptake intratracheally resembles parenteral administration more than oral or percutaneous exposure.

In man and experimental animals, factors which govern gastrointestinal absorption of arsenic include both the chemical form of the element and its physical characteristics. It can be stated that soluble arsenicals will be generally more extensively absorbed than the insoluble forms. On the other hand, one should be cautious in extending data for simple water solubility to the chemical milieu existing in the GI tracts of various species.

Taken collectively, the reports of Coulson, et al. (1935), Ray-Bettley and O'Shea (1975), Crecelius (1977), and Mappes (1977) demonstrate that very substantial gastrointestinal absorption of soluble inorganic trivalent arsenic occurs. Greater than 95 percent of inorganic arsenic taken orally by man appears to be absorbed, with less than 5 percent of the administered amount appearing in feces (Coulson, et al., 1935; Ray-Bettley and O'Shea, 1975).

Consistent with this, Mappes (1977) observed that daily intake orally of an aqueous solution of ~0.8 mg trivalent arsenic led to a daily urinary excretion rate of 69 to 72 percent of the daily intake by a human subject. Also, Crecelius (1977) reported that ingestion of 50 µg trivalent and 13 µg pentavalent inorganic arsenic in a wine sample led to 80 percent of the total 63 µg of arsenic appearing in urine within 61 hours. Crecelius (1977), however, reported that ingestion of well water mainly containing identified pentavalent inorganic arsenic led to urinary clearance of half of the intake of ~3 days. Absence of fecal arsenic data preclude determining fecal loss or body retention of the remaining half.

In contrast to the relatively high absorption rate for soluble inorganic arsenic, Mappes (1977) reported that insoluble arsenic triselenide (As_2Se_3), when taken orally, passes through the GI tract with negligible absorption.

While available data for human GI tract absorption of As_2O_3 taken up via inhalation are sparse, the report of Smith, et al. (1977) strongly suggests that levels of arsenic trioxide entering the GI tract of smelter workers strongly correlate with urinary arsenic levels.

Analysis of arsenic intake via the diet of nonoccupationally exposed populations requires that one consider the issue of bioavailability and differences in the manner in which arsenic forms are incorporated into the matrix of various foodstuffs. In terms of concentration levels and bioavailability factors, the arsenic content of crustaceans and other marine foods warrants special comment.

The so-called "shrimp" or "seafood" arsenic present in crustaceans and other fish appears to represent a complex organic form of the element which has recently prompted considerable study (LeBlanc and Jackson, 1973; Westoo and Rydalv, 1972; Munro, 1976; Edmonds, et al. 1977; Penrose, et al. 1977; Crecelius, 1977; Edmonds and Francesconi, 1977). In brief, the results of such studies indicate that the arsenic present in shellfish and other marine foods appears to be extensively absorbed and rapidly excreted intact as a complex organoarsenical by man and animals and, as such, does not appear to pose a particular health threat to man. Thus, it is not appropriate to consider high human arsenic intake from diets heavy with "seafood" arsenic as representing relevant exposure inputs for estimating the likely toxicity potential associated with overall exposure of population segments to inorganic arsenic via multimedia routes.

Studies of the oral intake and absorption of arsenicals in experimental animals generally confirm the findings derived from the above human studies. More specifically, soluble inorganic arsenic, in either trivalent or pentavalent solutions, is almost completely absorbed from the GI tract of rats (Coulson, et al. 1935), with 88 percent absorption was observed for arsenic trioxide solution (Urakabo, et al. 1975; Dutkiewicz, 1977) and 70 to 90 percent for arsenate solution. Similar observations have been made in pigs (Munro, et al. 1974), with 90 percent of arsenic trioxide solution being absorbed, and monkeys (Charbonneau, et al. 1978a) with 98 percent of arsenic trioxide being absorbed. Charbonneau, et al. (1978a) fed arsenic-containing fish (Atlantic grey sole) to adult female monkeys as a homogenate (1 mg fish arsenic/kg body weight) and noted that about 90 percent was absorbed, of which about 75 percent appeared in urine after 24 days. In a related study, swine and adolescent monkeys were seen to absorb approximately 70 to 50 percent, respectively. On the other hand, arsenic trioxide in suspension given orally to rabbits and rats was reported to result in only about 40 and 30 percent absorption, respectively (Ariyoshi and Ikeda, 1974).

The effect of nutritional status or dietary factors on arsenic absorption has not been well studied, although interactive relationships between arsenic and elements such as selenium are known. Tamura et al. (1977) showed that rats given arsenic trioxide in either milk or cereal diets had no differences in fecal excretion patterns of arsenic over a 6-month period. Nozaki, et al. (1975), using ligated rabbit intestine, demonstrated that phosphate, casein, and a casein hydrolysate all inhibited trivalent arsenic uptake. Tsutsumi and co-workers (1976) found that co-administration of metal chelanting agents, such as dimercaprol (BAL), thioctic acid (TA), or diisopropylaminodichloroacetate (DADA), with ^{74}As labeled arsenate into the GI tract of the rat resulted in markedly retarded enteric absorption of the arsenical, compared to controls receiving the labeled arsenate alone.

Little information exists on the extent of cutaneous absorption into the bloodstream of inorganic arsenic by human subjects. Evidence for skin absorption sufficient to induce clinical manifestations of arsenic poisoning stems from case reports of either individual accidents with arsenic trichloride (Delepine, 1922,1923; Buchanan, 1962), arsenic acid solution (Garb and Hine, 1977), or (arsenical paste) (Robinson, 1975). Patty (1948) notes that arsenic passage through epidermal lesions is more rapid than with normal skin suggesting that, in the case of industrial activity, the skin burns elicited by arsenic contact permit easier passage of arsenic into the deeper layers of the integument.

Dutkiewicz (1977) found that skin absorption of arsenic in the rat using solutions of arsenate, was significant and the uptake rate via the tail was as high as 33.1 $\mu g/cm^2$/hour using concentrations up to 0.2 molar. The corresponding absorption in man, using 700 cm^2 as the surface area for both hands, was calculated to be as much as 23.2 mg/hour; and tissue levels of arsenic from dermal contact resembled the distribution dynamics of oral exposure.

Potential fetal exposure to toxic elements via transplacental passage from the mother is of major importance given the potential sensitivity of in utero development to diletarious impacts of exogenous toxic agents.

In a study of maternal-newborn tissue sets for arsenic, Kagey, et al. (1977) reported that cord blood levels approximate those of mothers in 101 subject sets. Tissue analysis (Kadowaki, 1960) of fetus arsenic in a presumably healthy Japanese population indicated measurable arsenic levels at least by the fourth month of gestation and increasing to the seventh month. Of importance here is the observation that brain levels, as well as those of bone, liver, and skin, were the highest of all tissue tested. Since the relative amounts of arsenic passing the blood-brain barrier in adult animals appears to be small relative to uptake in other soft tissues, these data suggest that the human fetal nervous system may be particularly vulnerable to arsenic exposure early in development.

Complicating the issue is the chemical nature of the tissue arsenic assayed in either of the two studies noted above, inasmuch as precise chemical speciation was not attempted. Also, the Japanese study presumably did not select material in a manner such that dietary histories could be discerned. Thus, questions can be raised regarding full implications of these data for toxicological analyses.

Transplacental transfer of arsenic has also been demonstrated in experimental animals. For example, rapid transplacental transfer has been demonstrated in hamsters given arsenate parenterally (Ferm, 1977; Hanlon and

Ferm, 1977), with embryonic tissues showing levels close to those in maternal blood 24 hours after dosing. Trivalent arsenic, given as such, also results in transplacental passage in pregnant rats. Arsenic has been detected in newborn rats when the dams received arsenic trioxide in the diet.

Distribution

Analysis of the available literature dealing with the tissue distribution of inorganic arsenic must be tempered by current awareness that in vivo biotransformations of arsenic occur in many species and distribution dynamics involve the transformation products as well as any intermediates or original exposure forms.

Blood is the main vehicle for transport of arsenicals from absorption sites to various tissues, with the hemokinetic character of arsenic being dependent on the animal species studied. It is readily apparent from the literature that the rat constitutes an anomalous model for studies of the fate of inorganic arsenicals in vivo and this includes the clearance behavior of blood-borne arsenic in the rat (Hunter, et al. 1942; Ducoff, et al. 1948; Lanz, et al. 1950; Ariyoshi and Ikeda, 1974; Klaassen, 1974; Tsutsumi and Kato, 1975; Dutkiewicz, 1977). In the case of the rat, arsenic in blood is only slowly cleared following exposure, with about 80 percent of the total blood arsenic content localized in the erythrocyte. The half-times of blood clearance for inorganic arsenic in the rat (trivalent or pentavalent) is of the order of 60 to 90 days (Lanz, et al. 1950; Ariyoshi and Ikeda, 1974). Given the recent data of Odanaka, et al. (1978), cited earlier, it is possible that erythrocyte arsenic is present as the dimethylated form.

Arsenic in the blood of other species -- man (Ducoff, 1948; Mealey, et al. 1959), mice (Lanz, et al. 1950; Crema, 1955), rabbit (Hunter, et al.

1942; Ducoff, 1948; Klaassen, 1974), dog (Lanz, et al. 1950; Hunter, et al. 1942), and the primate (Hunter, et al. 1942; Klaassen, 1974) -- whether given as the pentavalent form or as trivalent form, is rapidly cleared.

In some of these species, a three-compartment model for clearance is apparent. Overby and Fredrickson (1963) calculated half-times of ~6 hours for the rapid phase, a slightly longer time for the second phase and a slow phase of ~60 hours.

Clearance of arsenic in dog and man was also found to fit a three-compartment model by Charbonneau, et al. (1978b) with half-times of 1, 5, and 35 hours, respectively. When contrasted with the work of Tam, et al. (1978a), which reported the time dependent in vivo methylation of arsenic and excretion, the various components presumably relate to initial excretion of inorganic arsenic, followed by clearance of dimethylarsenic.

Very little information is available concerning the molecular character of binding in either erythrocytes or plasma, and what little older data is available must be viewed in the light of what is presently known about in vivo changes in arsenical forms.

In the rat erythrocyte, arsenic appears to be associated with the protein moiety of hemoglobin (Hunter, et al. 1942; Lanz, et al. 1950). Labeled arsenite (^{76}As), when given to a human subject, appeared to be associated in plasma with α_1-globulin (Musil and Dejmal, 1957).

Biliary transport of arsenic has been reported for a number of species. Bile excreted arsenic is reabsorbed. Cikrt and Bencko (1974) noted that the rat had a higher biliary excretion rate for trivalent than for the pentavalent form (~10:1). Klaassen (1974) noted that the biliary excretion rate was much greater for the rat than for either the rabbit or the dog. Biliary transport data for man is not available.

The tissue partitioning of arsenic in man has been studied using both autopsy and dosing data. Kadowaki (1960) found that heart, kidney, liver, and lung contained the highest levels of arsenic (0.04 to 0.05 ppm, wet weight) of the soft tissues, with skin, hair, teeth, bone, and nails -- arsenic storage organs -- housing the highest absolute amount. Brain tissue (0.03 ppm wet weight) had an arsenic level slightly lower than other soft tissue. Liebscher and Smith (1968), analyzing tissue samples from nonexposed sources in Scotland, observed lung to have the highest levels (0.08 ppm dry weight), with liver and kidney levels (0.03 ppm dry weight) not materially different from other soft tissue. Like the Kadowaki study, storage organs such as bone, hair, nails, and teeth had the highest overall levels.

In addition to the autopsy studies by Kadowaki (1960) and Liebscher and Smith (1968), Larsen, et al. (1979) have recently reported on a detailed study of the topographical distribution of arsenic in normal human brain tissue. The study results (for 5 persons, 15 to 81 years of age) revealed widespread distribution of arsenic throughout essentially all of 24 brain areas sampled, with markedly higher concentrations of arsenic in white matter (2.4-5.2 ng/g wet tissue) than in grey matter (1.2-2.6 ng/g wet tissue). These arsenic concentrations in central nervous system white matter are not significantly different from arsenic concentrations reported earlier for peripheral nerves (Larsen, et al. 1972), leading to the interpretation by Larsen, et al. that the metal is likely preferentially accumulated in neural tissue components (e.g., myelin) high in lipids, phospholipids, or phosphatides. This interpretation is consistent with the proposition by Schroeder and Balassa (1966) that arsenic has a predilection for accumulation in fat.

The above findings appear to be rather consistent in regard to the overall patterns of tissue distribution of arsenic based on human autopsy material. However, since the above studies were carried out with little attention to dietary histories, particularly the predominance of seafood in diet, it is difficult to compare the study results in absolute quantitative terms or to draw precise conclusions from them regarding trends in tissue accumulation with age. Kadowaki's data for infants and elderly subjects, nevertheless, suggest some age-dependent accumulation in skin and kidney. Also, the above studies do not provide a basis for assessing possible differential tissue distribution of tri- or pentavalent-inorganic arsenic. Other studies indicate, however, that when human subjects are exposed to trivalent arsenic parenterally, highest levels of arsenic are seen in liver and kidney (Hunter, et al. 1942; Ducoff, et al. 1948; Mealey, et al. 1959).

Exposure of various species to either tri- or pentavalent arsenic leads to the initial accumulation of the element in liver, kidney, lung, spleen, aorta, and skin (Hunter, et al. 1942; Ducoff, et al. 1948; Lanz, et al. 1950; Peoples, 1964; Ariyoshi and Ikeda, 1974; Cikrt and Bencko, 1974; Klaassen, 1974; Tsutsumi and Kato, 1975; Urakabo, et al. 1975; Dutkiewicz, 1977). With the exception of the rat, a species in which metabolism of arsenic is only a very limited model for study of this element (vide supra), clearance from soft tissue is rather rapid except for the skin, where the high sulfhydryl group content probably promotes tight arsenical binding. As also seen with human tissue, arsenic is apparently lodged in the brain of experimental animals exposed to arsenic, with slow clearance reported (Crema, 1955).

The more-or-less similar tissue distribution profiles for both tri- and pentavalent arsenic in various species probably reflects the common biotransformation pathways for inorganic arsenic that have been described earlier. It should be noted, however, that since presacrifice perfusion of animals in these studies was not carried out, part of the arsenic tissue burdens reported may be attributable to trapped blood. This might, for example, account for at least part of markedly elevated tissue levels noted for spleen.

Metabolism

The understanding of assimilation of inorganic arsenic by man and other mammalian species is substantially complicated by a series of newly-documented biotransformations, including methylation of inorganic arsenic. Therefore it is appropriate to discuss *in vivo* transformation processes at this point, since much of the data dealing with blood transport, tissue distribution, and subsequent excretion is much better understood in light of the newly emerging biotransformation findings.

A major factor in the determination of *in vivo* transformation processes for arsenic was the evolution of analytical methods allowing for chemical speciation of chemically variant forms of arsenic with reference to both oxidation-state lability and inorganic versus organo substituted arsenic. The features and relative utility of these analytic techniques have been extensively reviewed by Mushak (1977).

Using a method that permits the determination of tri and pentavalent inorganic arsenic as well as mono- and dimethylarsenic acids via selective reduction, volatilization and helium arc emission detection, Braman and Foreback (1973) analyzed the urinary excretion of arsenic in four human volunteers. About two-thirds of the total urine arsenic concentration was present as dimethylarsinic acid and 17 percent as pentavalent inorganic arsenic. Trivalent inorganic arsenic and methylarsonic acid were present in equal amounts, 8 percent each.

Crecelius (1977) reported the urinary excretion of form variable arsenic when a human subject ingested arsenic in known oxidation state or other chemical forms. Ingestion of a wine sample of known arsenic content and form (50 μg trivalent and 13 μg pentavalent) was followed in about 61 hours by major clearing of the 63 μg of arsenic: 50 percent as dimethylarsenic acid, 14 percent as monomethyl arsenic, and 8 percent each in the two inorganic forms.

Consumption of well water containing 200 μg arsenic as arsenate by a subject in the same study showed urinary trivalent arsenic at near background levels with an elevation in pentavalent form as well as increased excretion of dimethylarsenic. Determining exact percentages of each excreted form was complicated by recovery of but half of the ingested amount. Arsenic as contained in canned crab tissue was also studied in this experiment. It would appear that arsenic is present in marine foods in an organic form which is excreted intact, but from which dimethylarsenic may be liberated by chemical treatment.

The study of Smith, et al. (1977), using basically the same speciation/analysis techniques noted in the previous study and involving urinary profiles for a group of copper smelter wokers, also confirmed transformation processes in vivo (Table 5). In controls as well as in three study groups that varied as to intensity of airborne trivalent arsenic oxide exposure, dimethylarsenic was the dominant species in urine, followed by methyl arsenic, trivalent arsenic, and pentavalent arsenic.

Interestingly, the correlation of dimethylarsenic with airborne exposure composed a tighter fit than total arsenic. Furthermore, both fine respirable and larger (>5 μm) fractions of arsenic trioxide particulate correlated with all four forms measured, with a stronger relationship seen for the

TABLE 5

Concentration of Arsenic in Urine and Airborne Samples Test and Control Groups*

Urinary Species	Control (n=41)	As concn. (SD)[a] Low As Exposure (n=30)	Medium As Exposure (n=23)	High As Exposure (n=30)
AS (III)[a]	1.3(1.58)	2.2(2.19)	4.8(2.08)	8.6(2.62)
As (V)[a]	1.31(1.59)	1.6(2.32)	2.4(2.86)	3.1(3.64)
Methylarsonic acid[a]	3.4(1.63)	4.9(2.13)	9.7(1.90)	20.8(2.55)
Dimethylarsinic acid[a]	11.5(1.47)	17.0(1.96)	32.7(1.71)	64.1(2.42)
Total urinary arsenic	21.2(2.04)	24.7(2.01)	51.8(1.61)	66.1(2.14)
Arsenic[b]	3.6(1.56)	8.3(3.43)	46.1(3.05)	52.7(6.61)

*Source: Smith, et al. 1977

[a] All concentations are expressed as μg/l of elemental arsenic, geometric mean (standard deviation).

[b] All constituent concentrations are expressed as μg/m^3 geometric mean (standard deviation). Controls had 56.1 percent of samples less than detectable (<1.2 μg As/m^3) and the low group had 20 percent less than detectable.

larger portion, i.e., that portion which mainly enters the body via the GI tract. It may be seen that while the relative amount of dimethylarsenic acid, (which may be considered a detoxification form) is invariant over the various exposure groups, the relative amount of trivalent arsenic (particularly in comparison to pentavalent arsenic) increases almost linearly with increasing exposure. This increase in trivalent arsenic with increasing exposure to airborne arsenic is further suggestive evidence that it is the trivalent form of arsenic *in vivo* that mainly accounts for toxic effects seen in man and is consistent with dose-response relationships for various health effects found in epidemiologic studies.

Reports in the literature dealing with the interconversion of trivalent and pentavalent arsenic in man are sketchy. Mealey, et al. (1959) noted that administration of ^{74}As trivalent arsenic parenterally to human clinical subjects resulted in excretion of levels of "pentavalent" arsenic that ranged from about 60 percent 1 day post-dosing up to 80 percent with further time. The method employed involved the acidification of urine samples with hydrochloric acid followed by benzene extraction. Trivalent arsenic is extracted by benzene, but the pentavalent form remains. Since this separation approach differentiates tri- and pentavalent inorganic arsenic (later bioanalytically confirmed by both Mushak, et al. 1977 and Reinke, et al. 1975) as well as methyl arsonous from methylarsonic and dimethyl arsinous from cacodylate (Mushak, et al. 1977), it is probable that the "arsenate" fraction was a mixture of cacodylic, methyl arsenic, and inorganic pentavalent arsenic. Since the amount of "arsenate" determined was greater proportionally than any contaminating level in the parenteral dose, conversion to arsenate and methylated forms had occurred.

One subtle aspect of this report, however, is that mono- and, more importantly, dimethylarsenic in these urine samples existed as dimethylarsenic (cacodylic) rather than dimethylarsinous acid. Were the case otherwise, i.e., methylated arsenic in lower oxidation state, then extraction into benzene from hydrochloric acid solution of the lower-state methyl arsenicals would have occurred, as indicated by the observations of Mushak, et al. (1977). This does not preclude the possibility that sufficient oxygenation of urine samples occurs in the process of collection to allow oxidation *in situ*, but the work of both Smith, et al. (1977) and Crecelius (1977) indicates that whatever artifactive oxidation in urine post-collection may occur, at least measurable inorganic trivalent arsenic remains and at levels proportional to exposure to the trivalent form.

A number of animal studies also provide data regarding the character and quantitative aspects of *in vivo* transformation processes of inorganic arsenic. Of necessity, the weight placed on these studies is tied to the quality of the methods of analysis and their ability to chemically speciate the various forms. This also necessitates retrospective scrutiny of methods used in the earlier literature since the more reliable speciation techniques are of recent origin.

To date, transformation processes involving arsenic and experimental animals have been reported for the dog (Lakso and Peoples, 1975; Tam, et al. 1978,1979; Charbonneau, et al. 1979), cow (Peoples, 1964; Lakso and Peoples, 1975), mouse (Bencko, et al. 1976), and rat (Winkler, 1962; Ginsburg, 1965; Odanaka, et al. 1978).

Lakso and Peoples (1975) noted that the oral exposure of both dogs and cows to either arsenite or arsenate led to conversion of either valency form to methylated arsenic with about 50 percent conversion to methyl arsenic, which may formally be considered pentavalent. The method used did not permit distinction between valency forms of inorganic arsenic.

Several more recent studies have provided more detailed data as to arsenic transformation processes in the dog. Tam, et al. (1978,1979) exposed a group of dogs to radiolabeled (^{74}As) arsenic acid given intravenously. The levels of inorganic, monomethyl-, and dimethylarsenic were then timemonitored in urine and plasma using an ion-exchange chromatographic technique. While inorganic arsenic is the major species in plasma up to about 2 hours post-dosing, dimethyl arsenic formation can be detected as early as 10 minutes after administration. By 6 hours, virtually all (90 percent) plasma arsenic is in the dimethyl form, with little monomethyl species detected. Dimethylarsenic was the major form in the urine from days 1-6. In a companion study, Tam, et al. (1978b) used thin-layer chromatography to further speciate the inorganic arsenic fraction into both pentavalent and trivalent arsenic. Charbonneau, et al. (1978a,b) noted that when labeled arsenic acid (^{74}As) was given to dogs intravenously, about four-fifths of the arsenic lodged in the red cells, with dimethylarsenic being detected in those cells about 10 minutes after dosing. With time, the arsenic content is partitioned between cells and plasma, total conversion being seen by 6 hours. At about 1 hour, dimethylarsenic is detected in the urine. These data indicate participation of the erythrocytes and liver in dimethylation and transport of the dimethylated species.

Of interest, here are the data of Odanaka, et al. (1978), who fed ferric methanearsonate to adult male rats and analyzed the blood, urine, and feces for the amount of various speciated arsenical forms. Dimethyl arsenic was detected in urine, feces, and blood, indicating methylation of monomethyl arsenic in vivo. While dimethylarsenic was in minor amounts in urine and feces, blood arsenic was mainly present as dimethylarsenic. For analysis, these workers used thin-layer chromatography for separation of the arsenicals and gas-liquid chromatography in tandem with mass spectrometry to conclusively determine the structure of the organoarsenicals as mono- and dimethylarsenic.

The Odanaka, et al. (1978) paper is of significance on several counts: (1) it demonstrates that methyl arsenic can be methylated to dimethylarsenic and, hence, the monomethyl form can be an intermediate in the inorganicdimethylarsenic transformation (since these authors took pains to assure the purity of the methyl arsenic administered, it is unlikely that the dimethyl form arose from contaminating inorganic arsenic); (2) mass spectral analysis confirms the presence of dimethylarsenic in arsenic transformations in the rat and, by inference, other animal models reported; (3) the minor amounts of dimethylarsenic in urine or feces and the major amounts in blood suggest selective retention of dimethylarsenic by rat erythrocytes. When contrasted with the Charbonneau, et al. (1978a,b) data noted previously, it appears that in both rat and dog the erythrocyte is at least the transport vehicle for dimethylarsenic, but, unlike the dog erythrocyte, release of dimethylarsenic into rat plasma is much slower. This is consistent with other known facts of arsenic distribution in the rat as noted below.

In light of the preceding reports regarding methylation processes, earlier reports dealing with trivalent-to-pentavalent-arsenic conversion or the reverse must be viewed carefully.

In vivo conversion of trivalent inorganic arsenic to the pentavalent form has been reported by several authors. Infusion of arsenite (trivalent) intravenously in dogs led to the detection of tri- and pentavalent arsenic in plasma, urine, and glomerular filtrate (Ginsberg, 1965). Winkler (1962) noted that livers of rats fed arsenite contained mainly arsenate. The more recent study of Bencko, et al. (1976) is particularly significant in that trivalent arsenic conversion to the pentavalent form in mice was demonstrated using paper chromatographic techniques for separation and removal of urine samples through the bladder to minimize artifactive oxidation of trivalent arsenic. It was noted that the relative amounts of pentavalent arsenic formed from radio-isotopic (^{74}As) arsenite hinged on the time lapse after pretreatment with a large dietary level (250 mg/l) in drinking water. In animals preexposed for 18 days prior to dosing with the labeled arsenate, virtually no trivalent arsenic was found in urine. Since dimethylarsenic acid was not tested in Bencko's chromatographic system, it is possible that this was the form being identified as pentavalent inorganic arsenic.

The case for *in vivo* reduction of pentavalent arsenic to the trivalent form is sketchier, mainly due to analytical methods employed. The approach of Lanz, et al. (1950), who reported some reductive conversion of arsenate, entailed precipitation as a mixed salt, the residual solubility of which could have been enough to account for the amount labeled as soluble trivalent arsenic (NAS, 1977a). The Ginsberg (1965) report employed an extraction/chelation separation method involving acidified samples and removal of trivalent arsenic with chloroform containing ethyl xanthate. Since ethyl xanthate is a thiolic chelanting agent and pentavalent arsenic is very labile in acid, interaction of the chelating agent with pentavalent arsenic to form arsenic (III) and some disulfide (R-S-S-R) cannot be discounted. Using dogs dosed with arsenate, the origin of the trivalent portion of the inorganic arsenic fraction as isolated and measured, i.e., *in vitro* versus *in vivo* formation, cannot be definitely established (Tam, 1978).

As can best be presently determined, demethylation of methylated arsenics formed *in vivo* does not occur. Support for this is chiefly from data of Stevens, et al. (1977), who saw no evidence of *in vivo* demethylation when animals were exposed to dimethylarsinic acid (cacodylic acid).

Several experimental animal studies suggest that some induction of a tolerance to arsenicals may arise in arsenic pretreated animals that are re-exposed. Bencko and co-workers (Bencko and Symon, 1969, 1970; Bencko, et al. 1976) have found that arsenic pretreatment of mice will markedly alter the subsequent tissue distribution and excretion data of a radio-isotopic arsenic pulse. The mechanism of this process is not understood, but must include the efficiency of the *in vivo* methylation process(es) described earlier.

In summary:

1. Pentavalent and trivalent arsenic in both man and animals undergo *in vivo* transformation mainly to dimethylarsinic acid, which probably was misidentified as pentavalent inorganic arsenic in early studies.
2. The *in vivo* conversion of pentavalent inorganic arsenic to the trivalent forms remains to be conclusively demonstrated, but cannot be ruled out based on presently available information.
3. Methylation of inorganic arsenic can be considered as detoxification in that cacodylic acid is much less toxic than the inorganic forms.
4. As a detoxification process, methylation efficiency appears constant as a fraction of total speciable arsenic, although the relative amount of trivalent arsenic will increase with increasing exposure.

5. However, as a detoxification process, it can eventually be overwhelmed or modified as is apparent from the extensive literature on arsenic toxicology in man and animals.
6. At least in some species, dimethylarsenic formation involves the erythrocyte and the liver in biosynthesis and transport.

Excretion

Renal clearance appears to be the major route of excretion of absorbed arsenic in man and animals, biliary transport of the element leading to enteric reabsorption with little carriage in feces.

In a study assessing the utility of urine arsenic measurement in occupational exposure settings, Mappes (1977) reported excretion data for both single and multiple daily dosing for a human subject ingesting arsenite solution. By 3 hours, renal excretion was maximal, with about one-quarter of the single dose appearing in the urine by day 1 post-exposure. With successive arsenite ingestion (0.8 mg As), daily urinary clearance after 5 days was two-thirds of daily intake.

Crecelius (1977) noted that arsenic in wine [50 μg As (III), 13 μg As (V)] after ingestion led to a measured level in urine of ~80 percent after 61 hours. Oral ingestion of arsenic (V) in well water (200 μg), however, led to about 50 percent urinary excretion by 3 days after ingestion. Mealey (1959) measured urine arsenic in patients given trivalent arsenic by intravenous administration, with ~60 percent of the dose amount appearing in the urine by 24 hours. Hunter, et al. (1942) noted considerable variance, 30 to 80 percent after 4 to 5 days, in urinary clearance of arsenic given parenterally in a group of human subjects.

As might be predicted from the *in vivo* behavior of arsenicals in the rat, urinary excretion of arsenic in this species is very slow, due to erythrocyte retention on the order of 2 to 5 percent of the arsenic intake by several days post-dosing (Coulson, et al. 1935; Ariyoshi and Ikeda, 1974). Urakabo, et al. (1975) calculated a half-time of 84 days for arsenic in the rat.

Slow clearance of arsenic from the rat gave rise to the widely held assumption for many years that arsenic is one of the elements that accumulate in the body. Other species excrete arsenic rapidly. Mice, rabbits, swine, dogs, and monkeys clear the majority of injected trivalent arsenic within 24 hours, with excretion usually being $\geq$70 percent within that time period (Ducoff, et al. 1948; Crema, 1955; Munro, et al. 1974; Lakso and Peoples, 1975; Tam, et al. 1978a; Charbonneau, et al. 1978b). Other studies also indicate rapid urinary clearance of arsenic given in the pentavalent form to species other than the rat (DuPont, et al. 1942; Ginsberg and Lotspeich, 1963; Peoples, 1964; Lakso and Peoples, 1975). Some calculated half-times for either tri- or pentavalent arsenic urinary clearance are: mice, injected trivalent, ~4.5 hours; dogs and cows, oral tri- or pentavalent, ~36 hours.

Deposition of arsenic in such organs as hair and nails can be considered an excretory mechanism for arsenic. Although hair analysis has had a long history in arsenic's chemical and forensic literature, for reasons of both analytical convenience and the possibiility of establishing an exposure history from sectional analysis, many questions remain unanswered. The relationhsip between arsenic deposition in hair and various exposure parameters has not been well defined on a quantitative basis nor are the physiological mechanisms well understood. The chemical nature of hair arsenic is also largely unknown.

The long-held view of arsenic as an element that accumulates in the body was mainly based on the behavior of arsenic in the rat, an animal model which in retrospect was the least helpful in understanding the fate of the toxicant *in vivo* for other mammalian species and man.

Based on current arsenic elimination data for all mammalian species studied other than the rat (*vide supra*), one concludes that marked long-term accumulation of arsenic generally does not occur in physiologically vital components of the body. This is in contrast to, say, marked long-term lead accumulation in bone or cadmium accumulation in renal cortex. Autopsy tissue data for human subjects of different ages is not conclusive regarding possible long-term tissue accumulation. Kadowaki (1960) did observe higher mean levels of arsenic in skin and kidney samples of subjects about 50 years of age versus infant values, but dietary histories of the subjects were not available to allow for differentiation of increases in arsenic levels due to current versus past exposures for the older subjects. Deposition in hair is really excretory in nature, not accumulative.

Brune, et al. (1980) have reported that lung tissue from retired smelter workers, on autopsy, had median values for arsenic which were approximately 8 times higher than that for a control group. Kidney and liver values, however, were not significantly different between smelter worker groups and controls. Arsenic accumulation in the lung of smelter workers even after several years of retirement and removal from workplace exposure (interval of 2-19 years) suggests that a very insoluble form of arsenic exists in smelter ambient air and is inhaled by these workers. That this form may be arsenic sulfide is further suggested by the study of Smith, et al. (1976) who found that the respirable air within the confines of a copper smelter contained arsenic sulfide. These two studies have implications for the issue of occupational respiratory carcinogenesis associated with arsenic exposure.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The multiplicity of organ systems and tissues affected in the manifestation of clinical symptoms of acute poisoning and in the production of systemic health effects associated with subacute or chronic exposure to the metal reflect well the widespread impact of arsenic in certain subcellular/biochemical processes common to cellular components of many different types of tissues. At the same time, certain distinctive features of arsenic systemic toxicity, e.g., its marked effects on the skin, are better understood in light of the intercession of the metal into particular biochemical processes most intensely characteristic of selected cells or tissue types, e.g., those comprising the integumentary system. The possibility of arsenic playing a beneficial role, at very low trace levels, as hinted at by newly emerging evidence for its essentiality in some mammalian species, is also best evaluated within the context of a discussion of the impact of the metal in subcellular/biochemical mechanisms.

The following discussion focuses on those data dealing with inorganic arsenic interactions at the biochemical and subcellular level which have the most relevance for understanding the *in vivo* toxic effects of the agent in man and experimental animals.

Several reviews (Peters, 1955; Vallee, et al. 1960; Johnstone, 1963; Webb, 1966) have described the effects of various arsenicals on enzymes and enzyme-mediated processes in a number of species. Many of these studies have entailed either purified preparations, where question of relevance to *in vivo* conditions can be raised, or heterogeneous, complex systems where the site of interaction(s) is left in doubt.

The literature dealing with effects of trivalent arsenic on enzymes is rather extensive, while that for pentavalent arsenic is considerably more sparse. This stems in large measure from the widely accepted fact that it is the trivalent form which can chemically interfere directly with enzyme action via formation of arsenic-sulfur bonds with those thiol groups which participate in either enzyme structure or function.

Webb (1966) has tabulated no less than 78 enzymes from a wide variety of species which have been reported to be inhibited to a varying degree by trivalent arsenic (arsenite) at concentrations of 0.01 to >10 millimolar. Although various classes of enzymes are sensitive to arsenite, the oxidizing enzyme systems appear to be particularly vulnerable, including: pyruvate oxidase, D-amino acid oxidase, 2-glutamic acid oxidase, monoamine oxidase, liver choline oxidase, and glucose oxidase.

Evidence in support of thiol binding as the biochemical site of enzyme inhibition includes: (1) all of the oxidase systems noted above can be reactivated with glutathione, a thiolic biochemical factor (Barron and Singer, 1943); (2) lipoic acid is a cofactor in a number of these enzyme systems and possesses proximal thiol groups expected to react readily with trivalent arsenic to form a highly stable five-membered heterocycle (Vallee, et al. 1960). Such effects not only provide good clues as to the biochemical basis for arsenic toxicity but also support the premise that arsenicals are general metabolic poisons.

One particularly important oxidizing enzyme systems sensitive to arsenic is the pyruvate dehydrogenase (PDH) complex which plays a crucial role in cellular energetics. The pyruvate dehydrogenase complex consists of three distinct enzymes: (1) pyruvate dehydrogenase (pyruvate decarboxylase), (2) dehydrolipoate transacetylase, and (3) dihydrolipoated hydrogenase. Arsenite could interfere with the latter two enzymes via binding to the proximal thiol groups of lipoic acid, while any effects on pyruvate decarboxylase are likely to be associated with the inactivation/activation reaction controlled by a phosphorylation/dephosphorylation process (Linn, et al. 1969).

Recently, Schiller, et al. (1977) studied the pyruvate oxidation system using liver mitochondria from rats fed pentavalent arsenic (up to 85 ppm As in drinking water) in order to pinpoint the site of arsenic interaction in the enzyme complex. Pyruvate dehydrogenase (enzyme 1 of the complex) activity was measured before and after activation *in vitro*. Basal activity before activation was reduced by 48 percent at 3 weeks in the animals fed 85 ppm As. The inhibition of pyruvate dehydrogenase activity both before and after activation suggests a direct effect on pyruvate utilization not involving lipoic acid.

Since the activation/deactivation process for PDH requires that phosphate bind at some point to both PDH and the phosphatase and kinase enzymes involved in activation/deactivation, arsenate presumably interferes by competing with inorganic phosphate. Thus, in this particular system, effects are imparted by both pentavalent (Schiller, et al. 1977) and trivalent arsenic (Webb, 1966). Inhibition of the PDH system by arsenic influences the operation of the tricarboxylic acid cycle, with decreased acetyl-Co A formation and subsequent decrease in NADH generated for ATP formation. Fatty acid synthesis and storage triglycerides are also affected.

Inorganic arsenic in the trivalent form has also been known to interfere with active transport processes and this literature has been critically reviewed by Webb (1966). Substance transport that is inhibited includes: potassium, sodium, rubidium, hydrogen ion, halide, monohydrogen phosphate, water, propionate, glucose, certain amino acids, marker dyes, and streptomycin. According to Webb (1966), it is difficult to ascertain whether arsenate has a specific effect on transport or whether the process reflects a general lesioning of cellular respiration by the arsenical. Some evidence suggests that the chief mechanism of transport inhibition involves pyruvate oxidation inhibition (Davenport, 1955).

Arsenite is known to be a potent inhibitor of chicken liver xanthine dehydrogenase and related molybdoflavoproteins (Rajagopalan and Handler, 1964, 1967; Peters and Sanadi, 1961; Palmer, 1962) and probably interacts with the molybdenum center in these enzymes (Coughlan, et al. 1969). Johnson and Rajagopalan (1978), using electron paramagnetic resonance (EPR) signal modification from molybdenum, found the site of arsenite interaction to be a reactive group within the molybdenum complex required for electron transfer from purine substrate to the enzyme and is probably a sulfhydryl unit binding the metal atom, a persulfide residue, or possibly the metal itself.

Although inhibition of enzymes due to arsenicals has been more heavily studied, enzyme activation by arsenicals is also known to occur (Webb, 1966). This includes activation of cytochrome oxidase of rat brain at an arsenate concentration of 1.0 millimolar, catalase malate dehydrogenase of pig heart at 30 millimolar and, apparently, enzyme systems associated with drug detoxification. For example, Ribeiro (1971) noted that trivalent arsenic oxide reduced hexobarbitone anesthesia time in mice although hexobarbitone oxidation and aminopyrene demethylation rates were unaltered. Also, Wagstaff (1978), studying the effects of dietary arsenic trioxide on hexobarbitone sleeping time, oxidation cleavage of O-ethyl-O-p-nitrophenyl phenylphosphonothioate (EPN), and O-domethylation of p-nitroanisole in rats at 100 to 5,000 ppm As, found moderate enzyme induction by trivalent arsenic but phenobarbital induction of the enzyme system was unaffected.

Unlike arsenite, pentavalent arsenate appears to exert biochemical effects via interference with phosphate transport and phosphorylation (NAS, 1977a; Fowler, et al. 1977), through uncoupling of mitochondrial oxidative phosphorylation, presumably via competitive replacement of inorganic phosphate by arsenate to form a highly labile arsenate ester that decomposes. Also, arsenate stimulates succinate-controlled respiration of rat liver mitochondria, an effect retarded by addition of phosphate (Crane and Lipman, 1953); and mitochondrial ATPase is stimulated by arsenate (Azzone and Ernster, 1961; Wadkins, 1961), the stimulation being offset by inorganic phosphate. Arsenate inhibition of mitochondrial respiration may occur via competition with phosphate during oxidative phosphorylation and/or inhibition of NAD reduction by succinate (Mitchell, et al. 1971). Rats chronically exposed to arsenate show decreased state 3 respiration and respiratory control ratios in renal and liver mitochondria (Brown, et al. 1976), associated with swelling of the organelle in both organs.

From the above, it can be seen that the mitochondrion is one cellular organelle particularly vulnerable to the effects of inorganic arsenic either as arsenite or arsenate (Webb, 1966; Fowler, 1977a; NAS, 1977a). Mitochondria readily take up arsenic and various *in vivo* and *in vitro* studies indicate that biochemical lesioning includes NAD-coupled mitochondrial respiration, uncoupled oxidative phosphorylation and interference with steps in the heme biosynthetic pathway which are intramitochondrial (Fowler, 1977b).

Arsenate causes mitochondrial swelling both in vitro (Packer, 1961; DeMaster and Mitchell, 1970; Mitchell, et al. 1971) and in vivo (Fowler, 1974, 1975; Brown, et al. 1976). Effects on liver mitochondria after prolonged oral exposure of rats to arsenate (20, 40, 85 ppm in drinking water) were found by Fowler et al. (1977) to include pronounced in situ mitochrondrial swelling in the 40 and 85 ppm-As exposure group animals, as well as lipidic vacuolization and fibrosis. These structural changes were associated with: (1) decreased state 3 respiration and respiratory control ratios for pyruvate/malate but not succinate; and (2) marked increase in specific activity of monoamine oxidase and cytochrome oxidase, sited in inner mitochondrial membranes. Effects of arsenate on these membrane marker enzymes suggests direct interaction with membranes, resulting in increased permeability or conformational change. The mechanism of these effects is probably arsenate interference in phosphorylation processes required for functioning of pyruvate dehydrogenase, the first enzyme in the pyruvate oxidation complex (Schiller, et al. 1977).

In a related study, Woods and Fowler (1977) saw a pronounced effect of oral arsenate administration (1.2, 2.2, and 3.5 mg As/kg; 6 weeks) on rat mitochondrial heme biosynthesis, with heme synthetase activity decreased to 63 percent of control levels at the highest exposure level, 3.5 mg As/kg, and a resulting porphyrin urea.

Incubation of respiratory rat liver mitochondria with arsenate for 20 minutes at 2°C followed by removal of the agent results in uncoupled respiration with succinate (Bhuvaneswaran, et al. 1972). Since most of the arsenate in this study was removed prior to oxidative phosphorylation assay, uncoupling of succinate oxidation is not an arsenolytic process. Interestingly, the mitochondrial preparation was capable of limited glutamate/malate or

3-hydroxybutyrate oxidation (ADP/O values of 1.3 to 1.6). Further study of this system (Bhuvaneswaran and Wadkins, 1978) indicates that arsenate treatment preferentially decreases the coupling capacity of mitochondria at sites 2 and 3. In related work, Bhuvaneswaran and Wadkins (1977) found that a small fraction of arsenate added to the mitochondrial preparation could not be removed even with trichloroacetic acid treatment. Since arsenic binding does not occur with cyanide, oligomycin, or inorganic phosphate, the binding is associated with an electron transport chain and energy-coupling reactions. Dissociation of the complex could be achieved after partial restoration of oxidative coupling at sites 2 and 3, i.e., ATP addition.

Harris and Achenjang (1977) found that uptake of arsenite by rat liver mitochondria to be energy-dependent and inhibited by mersalyl or N-ethymaleimide. Two modes of uptake were kinetically discernible and may involve both membrane thiol attachment and accumulation of free or bound arsenite in matrix space.

Fowler et al. (1978) studied microsomal and mitochondrial oxidative interactions in preparations from livers of rats exposed orally to arsenate (40 ppm in drinking water, for 6 weeks). Morphometric studies showed a doubling of the ratio between rough endoplasmic reticulum surface density and mitochondrial volume density in the arsenic treated animals. Microsomes from arsenic-treated animals contained 20 percent less aminopyrine demethylase activity compared to controls after mixing with mitochondria from control animal livers. These data point to an in vivo functional interaction between mitochondria and microsomes with regard to oxidative processes, with arsenate disturbing mitochondrial NAD-linked oxidative capability and reducing microsomal mixed-function oxidative capability.

In addition to characterization of mitochondrial effects, numerous studies have focused on the interaction of arsenic with DNA as it relates to chromosomal effects. Knowledge that arsenate can compete with phosphate in phosphorylation processes, as noted earlier, has prompted suggestions that arsenate occasions chromosomal abnormalities by substituting for phosphate in the DNA chain (Petres and Hundeiker, 1968; Petres, et al. 1970). This hypothesis ignores the fact that arsenate esters are so much more labile thermodynamically than the phosphorus analogs that it is questionable if such esters have other than transitory existence.

More likely is interference with DNA repair processes. Jung (1969, 1971) demonstrated decreased DNA repair following ultraviolet irradiation and incubation of skin grafts in arsenate solution, concluding that "dark repair" of DNA in these cells is inhibited. Results of studies by Rossman, et al. (1977) on effects of UV light and arsenite on strains of E. coli differing in DNA repair functions further implicate arsenite as interferring with DNA repair processes. Observations by Grunicke, et al. (1973) that DNA removal from tumor cells is retarded by either arsenate or arsenite suggests that cross-linking of DNA and protein may be occurring.

In regard to the possible role of arsenic as an essential element at low trace levels, early reports attempting to show a nutritional requirement for the element in animals were inconclusive (NAS, 1977a; Underwood, 1977). Part of the problem was undoubtedly technical in nature, i.e., the difficulty of carrying out such studies in an experimental environment where rigorous exclusion of a ubiquitous element from the diet is necessary. More recently, however, several carefully controlled studies appear to demonstrate nutritional essentiality for arsenic in some mammalian species. For example, Nielsen, et al. (1978) observed that feeding of arsenic-deficient diets to pregnant rats resulted in greater perinatal mortality among pups from arsenic-deprived dams and post weaning deficits in growth, enlarged spleens, and increased red cell osmotic fragility.

Anke, et al. (1978) also studied nutritional requirements for arsenic, using goats and mini-pigs and a semi-synthetic diet containing less than 50 ppb arsenic. Effects attributed to arsenic deficiency in both species occurred in adult animals and their offspring. Arsenic deficiency increased the mortality of adult goats as well as altering their mineral profiles for copper and manganese. Significant reproductive effects for both arsenicdeficient goats and mini-pigs included reduction of normal birth percentages and litter sizes; and the mortality of kids and piglets from the As-deficient groups was significantly increased. Manganese levels were elevated in As-deficient kids and piglets, but no perturbation of hematological indices (hemoglobin, hematocrit, or mean corpuscular concentration) was noted.

This is in contrast to observations with rat (Nielson, et al. 1974), where decreased hematocrits, elevated iron content in spleen, and increased osmotic fragility of cells were seen. Given that the rat is known to be an anomalous animal model for arsenic metabolism (see Metabolism section) however, these differences are probably peculiar to that species. Other evidence for the likely essentiality of arsenic in the rat, includes the findings of Schwartz (1977), who noted enhanced growth effects of arsenite on rats fed an arsenic-supplemented diet. An optimal effect was seen at 0.25 to 0.5 ppm, but pentavalent arsenic as sodium arsenate was less effective.

Despite the above evidence for possible arsenic essentiality in some mammalian species, any physiological role for arsenic, the existence of any specific carrier agent in the body, or other evidence of arsenic essentially in man remains to be independently demonstrated. Another factor complicating the issue is the fact that one usual feature of essential element metabolism is homeostatic control of levels and movement of a particular element *in vivo*. Based on information considered earlier, there appears to be no effective absorption barrier for most soluble inorganic arsenicals, but efficient excretory mechanisms (kidney, hair) and biotransformation appear to provide possible control over an absorption-excretion balance. The question of arsenic essentially in man is made even more interesting by the study of Liebscher and Smith (1968) (see Metabolism section), who showed that arsenic in human tissue appears in a log-normal distribution, a commonly observed biostatistical characteristic of environmental contaminants rather than essential elements. Put in terms of physiology, this says that contaminant levels occur in tissues in simple proportion to the level of exposure, i.e., not under homeostatic control. However, such a biostatistical criterion added to those of Mertz (1970) is complicated in the case of arsenic if one does not know the specific partitioning of various chemical forms both *in vivo* and in the human diet.

The more physiologically subjective issue of arsenic beneficiality, particularly to man, merits some comment because the distinction between beneficiality and essentiality is not always made. Given the historical toxicological character of arsenic in man and animals, beneficial effects from the past (or present) use of such "therapeutics" as Fowler's solution (arsenite base), and arsenic pastes have not always been considered in a framework of benefit-risk balance. The beneficiality of agents such as Fowler's solution has required that the margin of risk perhaps be too narrow between levels associated with both beneficial dose-effect and toxicity dose-effect responses. By contrast, the limited data on arsenic essentially suggest a requirement for only very small trace amounts, leaving a huge gap between essentiality and toxicity.

The question of possible beneficial effects of arsenic also substantially involves the issue of interactive effects between arsenic and other substances, including certain important protective effects exerted by arsenic in relation to reducing toxicity effects associated with excess exposure to certain other trace metals.

Acute Toxicity

The typical systemic manifestations of arsenic poisoning due to ingestion usually include gastrointestinal disturbances (Dreisbach, 1971). The intensity and onset of symptoms are determined to some extent by the physical form of the arsenical, quantity ingested, and whether or not a meal has been recently eaten. Hemolysis is the primary manifestation of arsine poisoning.

The first symptom of acute poisoning is often a feeling of throat constriction followed by difficulty in swallowing, epigastric discomfort, and violent abdominal pain accompanied by vomiting and watery diarrhea (Buchmann, 1962). Intense thirst is usually present (Rentoul and Smith, 1973). Cramps may be present in muscles of the lower limbs. Systemic collapse with severe hypotension probably reflects widespread damage to the muscular system. Death which is generally preceded by restlessness, convulsions, or coma, may result from cardiac failure. In subacute poisoning, symptoms are less intense. If death is not immediate, jaundice and oliguria or anuria occur after 1 to 3 days (Dreisbach, 1971). The toxic action of arsenic on the gut lining epithelium is seen microscopically as a cloudy swelling and fatty infiltration (Buchmann, 1962). In less severe cases of occasional occupational exposure, recovery often occurs and may either be complete or followed by recurrent manifestations of symptoms characteristic of chronic poisoning.

Subacute and Chronic Toxicity

Several reports of acute arsenical posioning by ingestion have been cited in the older literature (Reynolds, 1901; Mizuta, et al. 1956; Takanehara, et al. 1956; Yoshikawa, et al. 1960). An acute poisoning episode also occurred more recently in two Indonesian orphanages from the ingestion of arsenic-contaminated rice which was prepared independently in each orphanage (Tjaij and Aziz, 1971). Laboratory analyses showed small amounts of arsenic in the urine of five children and in the vomit of one child. Symptoms of vomiting, abdominal pain, diarrhea, lassitude, dizziness, and headache appeared in 109 children and 48 adults 1 to 2 hours after ingestion of the rice. These symptoms were similar to these typically seen with the earlier incidents and accidental poisonings.

The acute oral toxicity of arsenic trioxide using commercial grade (97.77 As_2O_3 with 1.18 percent Sb_2O_3) and highly purified arsenic trioxide (99.99 percent As_2O_3) was tested in mice and rats by Harrison, et al. (1958). Test solutions were administered intraesophageally. For Webster Swiss mice, acute oral LD_{50} was estimated as 39.9 mg As/kg body weight for purified As_2O_3 and 42.9 mg As/kg body weight for the commercial grade. The LD_{50} for Sprague Dawley albino rats was 15.1 mg As/kg for the pure As_2O_3 and 23.6 mg As/kg for the crude form. While the LD_{50} for the purified arsenic was lower in both species, the purified arsenic was a less severe gastrointestinal irritant than the commercial form of arsenic trioxide. Retching and gastrointestinal damage were attributed to the presence of antimony in the unpurified preparation.

Several points regarding acute arsenic poisoning are of considerable interest. For example, trivalent arsenic is widely held to be more toxic systemically than the pentavalent form, based on both lethality data and sublethal experimental studies. Although it is rarely possible to establish precisely the exposure level in acute arsenic poisoning, Vallee, et al. (1960) have estimated a human lethality dose of trivalent arsenic as the oxide to be on the order of 70 to 180 mg. Individual susceptibility may be much less. Holland (1904) described one patient showing subacute symptoms to ~8 mg of arsenic in Fowler's solution (alkaline arsenite).

The matter of reversibility or nonreversibility of acute poisoning symptoms is also quite important. Survivors of acute arsenic poisoning display sequelae which involve the peripheral nervous, hematopoietic, cardiovascular, hepatic, and integumentary systems. The peripheral neuropathy, with an onset of several weeks, usually involves the lower extremities and histologically, is manifested by long axon Wallerian degeneration, and can persist for years (Ohta, 1970). Cardiac abnormalities range from certain electrocardiographic disturbances, included T-wave abnormalities, to eventual congestive heart failure.

The anemia and leukopenia of acute arsenic poisoning appear to be reversible features. These are in contrast to the longer-lasting symptoms such as skin lesions, including erythematous eruptions followed by pigmentation and keratoses of the extremities, which are late-emerging sequelae of subacute or chronic arsenic exposure. More detailed discussion of the organ systems involved in subacute and chronic arsenic toxicity is presented below.

Systemic exposure to amounts of arsenic sufficient to cause symptoms but inadequate to produce systemic collapse is of particular interest for development of human health criteria for arsenic exposure. The exposed patient may go for weeks or months with gradually increasing or variable signs and symptoms related to several organ systems and giving the appearance of a progressive chronic disease state. If death occurs, it may appear to have been the consequence of the inexorable course of an obscure "natural" disease. Information bearing on the induction of arsenic toxicity effects by subacute or chronic exposure of humans has been derived from case reports and epidemiologic studies of people exposed via use of therapeutic arsenicals, homicidal or accidental poisonings, and occupational or environmental exposures.

The literature describing the constellation of health effects observed in connection with various such exposure conditions or circumstances is briefly reviewed next, before assessment of salient information, including data on dose-effect or dose-response relationships, bearing on arsenic-induction of different specific classes or types of systemic health effects delineated by the organ systems affected.

Health effects associated with medicinal or therapeutic uses arsenicals have been best delineated in relation to the use of Fowler's solution. The method of arriving at a therapeutic dose of Fowler's solution is based on establishing a patient's tolerance to increasingly higher, but nontoxic doses of arsenic. As described by Holland (1904), the patient was typically given 5 drops (about 9 mg of arsenic trioxide, or 6.8 mg of arsenic) well diluted, after meals (i.e., three times a day), increasing the dose one drop daily until the disease is under control or until the eyelids puff and the bowels move too freely. The dose is then reduced to a safer quantity, and continued until the warning returns, when it is again reduced. For some persons even the minimum dose will produce unpleasant effects; one case of erythroderma has been reported after a patient received 10 mg of arsenic trioxide (7.6 mg of arsenic) taken over a 2-day period.

There are other case reports in the literature of subacute to chronic arsenic poisoning due to the use of Fowler's solution. Silver and Waimman (1952) described a patient who ingested approximately 8.8 mg of arsenic trioxide as Fowler's solution daily for a total period of 28 months, as a remedy for asthma. Signs of arsenic poisoning, manifested as increased freckling and as darkening of the nipples, first appeared in association with gastrointestinal symptoms after 13 months; redness and puffiness about the eyes and hyperkeratoses developed at approximately 1.5 years. Neurologic symptoms in the form of paresthesias and weakness were the last to be noted, occurring after 2 years. When the arsenic intake was stopped, the pigmentation lightened, but the hyperkeratoses remained, and the asthma became more difficult to control.

Also, Fierz (1965) examined 262 patients who had received long courses of medicinal arsenic 6-25 years previously and found keratoses in 40 percent and typical skin cancer in 8 percent. There was evidence of a dose relationship for both keratoses and skin cancer. Patients who had received more than 400 ml of Fowler's solution (4 g of arsenic trioxide) had an incidence of hyperkeratoses of greater than 50 percent, but as little as 60 ml (600 mg of arsenic trioxide) had resulted in keratotic changes in one patient. As little as 75 ml (750 mg of arsenic trioxide) had been consumed by one patient with skin cancer. The shortest time to cancerous change was 6 years, with an average of 14 years, compared with Neubauer's estimate of 18 years (Neubauer, 1947). Fierz (1965) noted that 1,450 invitations for a free examination had been sent to patients who had been given the therapeutic arsenic. Beside the 262 who came for examination, 100 patients provided written reports, and information was obtained about the deaths of 11. Five of the 11 deaths were due to systemic cancer, and three to lung cancer. Sixteen of the 21 patients with cancer had typical keratoses (Fierz, 1965).

In regard to health effects observed with homicidal and accidental poisoning cases, Holland (1904) used the information gained from personal observation and reports of suicide and criminal cases which used rat or fly poison, as well as Fowler's solution, to describe the effects of subacute and chronic arsenic exposure. Occasionally, enthusiastic patients would overdo their use of medicinal arsenic, but this was uncommon, because of the associated discomfort. Holland described subacute poisoning as producing loss of appetite, fainting, nausea and some vomiting, dry throat, shooting pains, diarrhea, nervous weakness, tingling of the hands and feet, jaundice, and erythema. Longer exposure resulted in dry, falling hair; brittle, loose nails; eczema; darker skin; exfoliation; and a horny condition (hyperkeratoses) of the palms and soles.

Mizuta, et al. (1956) reported on 220 Japanese patients of all ages who had been poisoned by contaminated soy sauce, with an average estimated ingestion of roughly 3 mg of arsenic (probably as calcium arsenate) daily for 2-3 weeks. In this group, 85 percent had facial edema and anorexia; fewer than 10 percent had exanthemata, desquamation, and hyperpigmentation; and about 20 percent had peripheral neuropathy. Except for headaches and fever, the findings in these patients appeared to be very similar to those reported by Reynolds (1901). Although the majority of patients' livers were enlarged, relatively few abnormalities were found in liver-function tests; and the histopathologic description of five liver biopsies did not reveal severe degenerative changes. There were no findings suggestive of congestive failure, but electrocardiograms were abnormal in 16 of 20 patients, and this confirmed the reports of Josephson, et al. (1951) and Nagai, et al. (1956). The symptoms tended to diminish after 5 or 6 days, despite continued intake of arsenic, and neurologic symptoms became prominent as much as 2 weeks after arsenic ingestion was discontinued, at which time urinary arsenic content remained high. Hair was found to contain arsenic at 2.8-13.0 µg/g near the root, compared with 0-1.5 µg/g near the end and 0.4-2.8 µg/g in hair from control patients.

For a few months in 1955, a large number of babies in Japan received a formula made from powdered milk contaminated with arsenic (Masahika and Hideyasu, 1973; Okamura, et al. 1956a,b; Satake, 1955).

The subacute symptoms of poisoning in these infants included the usual coughing, rhinorrhea, conjunctivitis, vomiting, diarrhea, and melanosis, but the striking presenting features were fever and abdominal swelling secondary to hepatomegaly. Abnormal laboratory findings included anemia, granulocytopenia, abnormal electrocardiograms, and increased density at epiphyseal ends of long bones similar to the familiar "lead line". Nagai, et al. (1956) reported on a group of these children who were followed for more than 6 months. Except for a measurable retardation in ulnar growth, they found that all other features of the syndrome had disappeared, including melanosis. Follow-up is continuing, and a report by the Japanese Pediatric Society (1973) indicated that growth was still reduced and that there was a probable incidence 15-30 percent of leukomelanoderma in the children (at the ages of 17-20 months). The children had a 15 percent incidence of keratosis (Yamashita, 1972). Of greater concern, however, was the observation of increased incidences of mental retardation, epilepsy, and other findings that suggested brain damage in the arsenic-exposed children. Presumably, future studies in this population (more than 10,000 exposed infants) will help to resolve some of the standing questions regarding the latent effects of arsenic exposure.

In regard to occupational arsenic exposures, it was noted by Perry, et al. (1948) that all of a group of chemical workers handling inorganic arsenic compounds had pigmentary changes and that one third of them had "warts," although these were not well described. They reported that the cutaneous "changes were so evident that (the examiner) could readily tell whether the man . . . was a chemical worker." All these workers had increased urinary arsenic compatible in degree with the extent of exposure; this indicates systemic absorption of the arsenic from dust, probably through the lungs and skin. High-exposure areas of the plant had arsenic concentrations ranging from about 250 to 700 $\mu g/m^3$.

Holmqvist (1951) also reported ezcematous and follicular dermatitis in smelter workers, primarily on exposed skin. Patch tests showed sensitivity to both trivalent and pentavalent arsenic. Birmingham, et al. (1965) reported similar lesions that developed within a few months of the startup of a gold smelter that handled ores containing large amounts of arsenic sulfide. Dermatitis developed in half the mill workers and in 32 of 40 students in a nearby elementary school.

Butzengeiger (1940) reported that, of 180 vinedressars and cellarmen with symptoms of chronic arsenic poisoning, about 23 percent had evidence of vascular disorders of the extremities. Arsenical insecticides were used in the vineyards, and exposure occurred not only with spraying, but during work in the vineyards by inhalation of contaminated dusts and plant debris. Sulfur and lime-sulfur were frequently applied in the same solution, or as a dust with lead arsenate. In either event, arsenite is formed as a function of the contact time between the two materials. Most of the workers consumed 1-2 liters of wine per day, especially that made from musk. It has recently been shown by Crecelius (1977) that wine contains high levels of arsenite from reductioan during fermentation. Wine made from the musk contains even higher levels of arsenite than normal. Exposure, therefore, to arsenite would seem to be convincing in this population, with lesser exposures of arsenate. All 15 workers with vascular disorders had hyperpigmentation, and all but two had palmer and plantar keratosis; six of the 15 had gangrene of the fingers and toes.

The same association of vascular disorders, hyperpigmentation, and keratosis was observed in Taiwan (Yeh, 1963). Urinary arsenic content average 0.324 mg/liter, and hair arsenic, 0.39 µg/g. Butzengeiger (1949) reported that the electrocardiograms of 36 of 192 vinegrowers with chronic arsenic intoxication were definitely abnormal, with no other evident cause. The abnormalities included prolongation of the Q-T interval and a flattened T-wave. In treated cases, these abnormalities diminished with the other evidence of toxicity. Similar findings were reported by Barry and Herndon (1962) and Glazener, et al. (1968).

Turning to health effects induced by various environmental exposures, in the early 1960s, physicians in Antofagasta, Chile, noted dermatologic manifestations and some deaths, particularly among children, that were traced to a water supply containing 800 µg/l of arsenic. This water supply had been in operation only since 1958. Borgono and Graiber (1972) have reported on studies of the inhabitants of this city. They compared 180 inhabitants of Antofagasta with 98 people who lived in a city (Iquique, Chile) with a normal water supply. Most of the people studied were less than 10 years old. Among the residents of Antofagasta the primary symptoms reported were abnormal skin pigmentation (80 percent); chronic coryza (60 percent); hyperkeratosis (36 percent); various cardiovascular manifestations, i.e., Raynaud's syndrome (30 percent); acrocyanosis (27 percent); abdominal pain (39 percent); chronic diarrhea (7 percent); and lip herpes (13 percent). The incidence of these symptoms in the control population was substantially lower or nonexistent.

Two additional reports on the Antofagasta studies are worthy of note. Zaldivar (1974) further described a study on a total of 457 patients (208 males, 249 females) bearing cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, squamous-cell carcinoma). Children (up to 15 years of age) accounted for 69.2 percent of male cases, and for 77.5 percent of female cases. These patients exhibited high arsenic content in the hair. The mean concentration of arsenic in drinking water in the period 1968-1969 was 380 µg/g versus 80 µg/g in 1971. Such difference was attributed to a new filter plant, which started operation in May, 1970. The average incidence rates per 100,000 population for cases with cutaneous lesions in 1968-1969 were 145.5 for males and 160.0 for females. The incidence rates decreased in 1971 to 9.1 for males and 10.0 for females.

Among the 337 registered children, 5 died showing thrombosis of brain arteries, thrombosis of mesenteric artery, restriction of lumen of coronary arteries, and/or myocardial infarction. Of the 64 registered adult males, 2 developed multiple skin carcinoma with lymph node metastases.

A number of questions are raised regarding this report. For example, the decrease in cutaneous lesions seemed to be too rapid, following installation of the water-treatment plant, suggesting other factors were involved. The 8- to 10-year-old age group recovered in three years. Adults exposed for more than 15 years also had a decrease in incidence rate of cutaneous lesions.

In a follow-up study, Borgano, et al. (1977) investigated clinical and epidemiologic aspects of the cases first reported in 1971. Arsenic content in hair and nail clipping samples of the inhabitants of Antofagasta were determined and compared to the levels measured in the initial study reported in 1971. Similar measurements and comparisons were performed for cultivated vegetables and carbonated beverages. Also, a clinical study was made in school children, looking for cutaneous lesions attributed to arsenicism. Six years after the water treatment plant started to operate the problem had diminished considerably. Arsenic determination of hair and nails of children 6 years of age or less, born since the water treatment plant went into operation, indicated no cutaneous lesions in this age group. However, those over 6 years of age still had significant arsenic residues in hair and nails. Although the clinical manifestations have improved, arsenic content of water, soft drinks, and in some foods are still considerably above safe levels and require additional sanitary engineering improvements.

Arguello, et al. (1938) reported on a large group of patients seen for arsenical skin cancers in the Cordoba region in Argentina, which had a high arsenic content in the drinking water (Bergoglio, 1964) and found keratoderma in 100 percent of the patients. Most patients also had associated hyperhidrosis and abnormalities of pigmentation, whereas those reported by Fierz (1965) did not. Arguello, et al. (1938) noted that the pigmentation appeared early and was variable among the patients. It was described as small dark spots 1 to 10 mm in diameter, with a tendency to coalesce, and appearing predominantly on the trunk, that is, in the areas not exposed to the sun. These and other authors have noted that atrophy may be associated with telangiectasia and loss of color, or leukoderma, between the hyperpigmented areas (the "raindrop" appearance) cited by Reynolds (1901).

In another study of large-scale environmental contamination exposure, Tseng, et al. (1968) surveyed a group of 40,421 residents of the southwest coast of Taiwan (from a population "at risk" of 103,154) exposed to arsenic via well water and found that they suffered from a number of dermatologic and peripheral vascular problems. The overall male and female prevalence rates for the clinical findings are as follows: hyperpigmentation 18.4 19.2 percent, 17.6 percent; keratotic lesions 7.1 - 7.5 percent, 6.8 percent; and black foot disease 0.9 - 1.2 percent, 0.7 percent for males and females respectively. The reason for the range of values for males was not explained. Skin cancer prevalence rates corresponded directly to age and arsenic exposure gradients (Table 6) (Tseng, 1977). The concentration of arsenic in the wells ranged from 17 to 1,097 μg/l. No cases of melanosis or keratosis were found in a group of 2,552 people living in an area where the wells contained almost no arsenic.

In considering arsenic health effects in terms of specific organ systems or tissues effected, the effects of arsenic on skin are clearly among the more notable and striking manifestations of the systemic toxicity of the metal. The characteristics of the skin malignancies found in chronic arsenism have been reviewed by Yeh (1963) and Yeh, et al. (1968) in their reports on the Taiwan cases. A prominant, even necessary, clinical feature of arsenical skin cancer is its association with the characteristic keratoses or pigment irregularities on the trunk. Several authors have cited a similar association in exposed workers as evidence that arsenic may cause internal cancers, especially of the lung (Braun, 1958; Currie, 1947; Hueper, 1951; Osburn, 1957; Robson and Jelliffe, 1963; Rosset, 1958; Roth, 1957). In addition, the skin lesions are characteristically multiple and predominantly on the areas of the body that are protected by clothing. Both these features are notable, inasmuch as "ordinary" skin cancers tend to be single and

TABLE 6

Prevalance of Skin Cancer for Males*

mg/l	20-39 yr (30)	40-59 yr (50)	>60 yr (70)
0 -0.29 (0.15)	0.0015	0.0065	0.0481
0.30-0.59 (0.45)	0.0043	0.0477	0.1634
≥0.6 (1.2)	0.0224	0.0983	0.2553

*Source: Tseng, 1977

have been shown to have a body distribution directly correlated with the amount of sun exposure (Birmingham, 1971; Miescher, 1934). Arsenical lesions (both keratoses and cancers) also appear at an earlier average age than do solar (senile) keratoses and related carcinomas (NAS, 1977a). The induction of skin lesions had been a characteristic result of oral ingestion of arsenic under all exposure situations discussed above.

The histopathology of the multiple and varied lesions seen in arsenism has been the subject of considerable interest among dermatopathologists (Anderson, 1932; Ayres and Anderson, 1934; Miescher, 1934; Montgomery, 1935; Pinkus and Mehregan, 1969; Yeh, 1963; Yeh, et al. 1968). Lesions that clinically are keratoses may show proliferation of keratin of a verrucous nature, may exhibit precancerous derangement of the squamous portions of the epithelium equivalent to those seen in Bowen's disease and solar keratosis, or may even be frank squamous cell carcinomas. Lesions that are less keratotic and more erythematous may contain either squamous cell or basal cell carcinoma or a mixture of cell types. Most authors seem to agree that keratotic lesions appear to be able to progress to frank carcinoma, but observation of such an event is rare, and most cancers appear to arise independently of the keratoses.

The question of the association of Bowen's disease with arsenism has stimulated considerable controversy. Graham and Helwig (1959) analyzed 36 autopsies of patients with Bowen's disease in whom arsenic intake had been ruled out as much as possible. It is striking that this group of patients differed from patients with arsenism in several respects: they lacked the typical keratoses and pigmentation; they had a tendency for the "typical Bowenoid" squamous cell carcinoma *in situ* to precede the other cutaneous malignancies by an average of 6 years; there was an incidence of approximately 80 percent of associated internal malignancies (some diagnosed only at autopsy); and they had suggestive evidence of a familial predisposition to the condition. Of more than 100 living patients with the dignosis of Bowen's disease surveyed by the same authors, internal malignancy had been diagnosed in 23. These features seem sufficient to distinguish Bowen's disease from chronic arsenism, despite the confusion later introduced by Graham, et al. (1961). If Graham and Helwig's cases are representative, the association of systemic cancers is much higher in Bowen's disease than has ever been suggested for chronic arsenism (NAS, 1977a).

The effects of arsenic exposure on skin may occur many years after cessation of exposure (NAS, 1977a). For example, Braun (1958) reported on 16 patients who had been exposed to arsenic in their occupation as vintners many years before. No known exposure to arsenic had occurred since. All had keratoses, nine had leukomelanoderma of the trunk, and seven had skin cancer or intraepidermal carcinoma _in situ_. Eight had lung cancer.

Roth (1957) also studied 47 vintners whose arsenic exposure had occurred 8-14 years earlier. His population was selected by having come to autopsy. He found that 33 of the 47 had cancer. A total of 75 malignant tumors (40 of which were skin cancers) of various tissues were observed: 18 cases had lung cancer, 6 with hemangiosarcoma of the liver, 5 with esophageal carcinima, and 1 with bile duct carcinoma.

Cardiovascular effects of arsenic have been demonstrated to occur with acute and subacute exposure of humans to inorganic arsenic and may include quite severe cardiovascular involvement, with congestive heart failure identified as a cause of death in fatalities encountered in one posioning outbreak (Reynolds, 1901). More recent clinical assessments of subacute and chronic arsenic poisoning of large numbers of people (Mizuta, et al. 1956; Hamamoto, 1955; Borgono and Greiber, 1972; Tseng, et al. 1968) indicate that the extent of cardiovascular injury with the nature of exposure, subject, geographic area, and level of arsenic intake.

Hamamoto's (1955) clinical findings of cardiovascular injury in 12,000 infants consuming arsenic-contaminated milk included elevation of the ST-wave and extension of the QT-interval, cardiographic changes which were slow to revert to normal after exposure and ceased. Similar cardiographic data for 200 patients who consumed arsenic-contaminated soy sauce were noted (Mizuta, et al. 1956).

In the clinical survey by Borgono and Greiber (1972) of both pediatric and young adult victims of chronic arsenic exposure via a drinking water supply, cardiovascular symptoms seen included Raynaud's syndrome, acrocyanosis, angina pectoris, hypertension, myocardial infarction, and mesenteric thrombosis.

Tseng (1968, 1977) described the incidence of "black foot disease" in Taiwanese consuming well water containing relatively high levels of arsenic. The disorder, a peripheral vascular derangement arising from arteriosclerosis and thromboangitis obliterans, results in gangrene of the feet and shows an increasing prevalence with increasing arsenic content of drinking water.

Chronic exposure to arsenic in occupational settings has also been reported to be associated with various cardiovascular disorders. Vine dressers who had been exposed to trivalent arsenic showed late onset (30 years post-exposure, exposure time of 20 years) peripheral vascular sequelae in the form of endangiitis obliterans and acrodermatitis atrophicans (Grobe, 1976). The role of arsenic in increased cardiovascular disease mortality is suggested by the epidemiological investigations of smelter workers by both Lee and Fraumeni (1969) and Axelson, et al. (1978).

Little information is available regarding useful animal models of the cardiovascular effects seen in arsenic-exposed human subjects. However, oral exposure (1.5 mg As/kg body weight) of cats to either arsenate or arsenite in feed (Massmann and Opitz, 1954) was followed by flattened T-wave and lengthened QT-time in the electrocardiogram.

Neurotoxic effects of arsenic have long been recognized as being associated with acute, subacute, and chronic exposures to relatively high levels of inorganic arsenic. These effects include both clinically significant peripheral nervous system (PNS) and central nervous system (CNS) damage reported as occurring in cases of accidental or homicidal arsenic poisonings, prolonged occupational exposures, and certain therapeutic applications of arsenical compounds. Such marked neurotoxic effects have been fairly well characterized in terms of their major pathophysiological features, clinical courses and sequalae, and associated histopathology. Much less well characterized are quantitative dose effect/dose response relationships defining arsenic exposure parameters associated with induction of neurotoxic effects in humans.

Reynolds (1901) provided one of the earliest detailed descriptions of arsenic-induced neurotoxic effects in reporting on clinical findings for more than 500 patients that had consumed arsenic-contaminated beer. As described elsewhere (NAS, 1977a), Reynolds (1901) reported that neurologic signs and symptoms began before the appearance of classical skin lesions, but followed such an insidious course of development so as to have gone undiagnosed for several weeks. Neurological involvement started with sensory changes, e.g., paresthesias, hypersthesias, and neuralgias, accompanied by considerable muscle tenderness. Varying degrees of motor weakness, progressing from distal to proximal muscle groups, also occurred and culminated at times in paralysis of affected muscle groups or extremities. Certain indications of central nervous system (CNS) damage, e.g., loss of memory and general mental confusion, were also observed but were discounted by Reynolds (1901) as being less likely due to arsenic than chronic alcoholism or concurrent excessive selenium intake.

Perpherial nervous system (PNS) effects similar to those described by Reynolds (1901) have since been observed in numerous other cases of acute, subacute, and chronic arsenic exposures (Silver and Wainman, 1952; Mizuta, et al. 1956; Heyman, et al. 1956; Jenkins, 1966; Hara, et al. 1968; Chuttani, et al. 1967; Ishinishi, et al. 1973; Nakamura, et al. 1973; Nagamatsu and Igata, 1975; O'Shaughnessy and Kraft, 1976; Frank, 1976; Garb and Hine, 1977; LeQuesne and McLeod, 1977) and are now recognized as classic clinical symptoms of arsenic poisoning. Such symptoms include peripheral sensory effects characterized by the appearance of numbness, tingling, or "pins and needles" sensations in the hands and feet, as well as decreases in touch, pain, and temperature sensations in a symmetrical "stocking glove" distribution. These symptoms are often variously accompanied by burning sensations, sharp or shooting pains, and marked muscle tenderness in the extremities. Peripheral neuritis symptoms originate distally and, over the course of a few weeks, often progressively become more widespread in both lower and upper extremities, usually appearing first in the feet and later in the hands. Signs and symptoms of peripheral motor nerve effects include: symmetrical muscular weakness of the extremities, predominantly distal but at times extending to proximal muscle groups and, rarely, the shoulder or pelvic girdle; evidence of foot and/or wrist drop; and, in some cases, rapidly developing paralysis and atrophy of lower leg muscles and small muscles of the hand.

Collectively, the above components of the classical clinical syndrome associated with excessive arsenic exposure are highly indicative of progressive peripheral polyneuropathy, involving both sensory and motor nerves, and most intensively affecting long-axon neurons. Several studies (Jenkins, 1966; Nagamatsu and Igata, 1975; O'Shaughnessy and Kraft, 1976; Garb and Hine, 1977; LeQuesne and McLeod, 1977) have provided quantitative electrophysiologic data, in the form of electromyographic (EMG) or nerve conduction velocity (NCV) recordings, confirming arsenic induced peripheral nerve functional deficits in association with the manifestations of frank clinical signs and symptoms of the above type. In addition, biopsy and autopsy studies have provided histopathological evidence verifying peripheral nerve damage, especially Wallerian degeneration of long-axon myelinated nerve fibers, in cases of human arsenic exposure where frank neurological signs and symptoms were manifested (Heyman, et al. 1956; Jenkins, 1966; Chuttani, et al. 1967; Ohta, 1970; LeQuesne and McLeod, 1977). Such degenerative changes in myelinated long-axon neurons are consistent with human autopsy findings discussed earlier regarding the uptake of arsenic into peripheral nerves (Larsen, et al. 1972) and preferential accumulation of the metal in CNS white matter with high content of "fatty" components of neural tissue, e.g., myelinated nerve fibers (Larsen, et al. 1979).

Several additional points regarding arsenic-induced peripheral neuropathies warrant special attention here for present health assessment purposes, including consideration of such issues as: (1) arsenical forms identified as inducing clinical neuropathies; (2) pattern(s) of development of neuropathic effects; (3) persistence of, available therapy for, and recovery from such effects; and (4) effective exposure or dosage parameters associated with their induction.

In regard to such issues, clinically-manifest cases of peripheral neuropathies have been demonstrated to occur as the result of exposure to many different inorganic arsenic forms under a variety of circumstances. For example, peripheral neuropathy effects have been documented in clinical cases of acute homicidal, suicidal, or accidental poisonings involving ingestion of various commercially available herbicides, pesticides, and animal poisons containing inorganic arsenic compounds such as: lead arsenate; sodium arsenate; calcium triarseniate; copper acetoarsenite (Paris Green); arsenious oxide; and arsenic trioxide (Heyman, et al. 1956; Jenkins, 1966; Ohta, 1970; O'Shaughnessy and Kraft, 1976). Similarly, peripheral neuropathy have been observed following acute, subacute, or chronic occupational exposures to many of the same arsenic compounds, e.g., in the course of agricultural applications of calcium or lead arsenate insecticide sprays, or occupational exposure to arsenicals such as: arsenious acid and other tri- and pentavalent inorganic arsenic compounds encountered in a coal gas desulfurization processing facility (Hara, et al. 1968); and arsenic trihydride or arsine (Frank, 1976). Thus, regardless of the particular inorganic arsenic form or valence state involved, it appears that excessive exposure to arsenic from any of the above substances can result in severe peripheral neuropathy.

In regard to the development and persistence of peripheral neuropathy associated with arsenic exposure, somewhat variable patterns of onset, persistence, and response to treatment have been observed, depending in part on the nature of specific exposure parameters. LeQuesne and McLeod (1977), for example, reported fairly rapid onset of peripheral neuropathies involving both motor dysfunctions and paresthesias, which appeared in four patients within 10 days to 3 weeks after ingestion of single large doses of inorganic arsenic compounds (e.g., sodium arsenate and arsenious oxide). Further deterioration occurred for a few days in 3 of the patients and progressively worsened for 5 weeks for the fourth, as indexed by NCV recordings and other observations of clinical signs and symptoms. All improved slowly thereafter, but after 6 to 8 years, 3 patients still had abnormal neurological signs and symptoms; NCVs, too, were still not in the normal range and marked atrophy of affected muscles was evident in some cases. The pattern of onset and persistence of neuropathy signs and symptoms observed by others (Heyman, et al. 1956; Jenkins, 1966; Nagamatsu and Igata, 1975; O'Shaughnessy and Kraft, 1976; Garb and Hine, 1977) for acute arsenic poisoning are consistent with those reported by LeQuesne and McLeod (1977); that is, the neuropathy typically become clinically manifest within a week or two after exposure and slow incomplete recovery is seen over a course of years, with some patients continuing to require the aid of leg braces to walk. Delayed onset of symptoms, 1 to 6 months after acute exposure to arsine has been reported (Frank, 1976) for six industrially exposed workers.

Under more chronic occupational exposure conditions to lower levels of arsenic compounds, the development of neuropathy symptoms can be more gradual and insidious and not only bilateral but unilateral polyneuropathies without motor paralysis have been reported (Ishinishi, et al. 1973; Nakamura, 1973). Again, the time course for recovery from the neuropathies, once induced, tends to be slow and on the order of years. Gradual onsets of peripheral neuropathies and slow recoveries have also been reported with subacute or chronic exposures to arsenic via ingestion of contaminated soy sauce (Mizuta, et al. 1956) or anti-asthmatic herbal preparations containing arsenic trioxide or asenic sulfide (Tay and Shea, 1975).

In regard to effective dosage parameters for induction of peripheral neuropathies by arsenic, it is usually not possible to determine precise doses involved or periods of exposure. For most acute poisonings, it is usually evident that high level exposure (on the order of tens or hundreds of mg or more) occurred, frequently involving only a single dose. For subacute or chronic poisoning situations, information exists from few studies by which effective exposure parameters can be estimated. Mizuta, et al. (1956), for example, reported that peripheral neuropathies occurred in 20 percent of 220 patients of all age groups poisoned by ingestion of arsenic contaminated soy sauce, with approximately 3 mg arsenic (likely as calcium arsenate) estimated to be ingested daily for 2-3 weeks resulting in total effective doses up to approximately 60 mg. Also, Tay and Shea (1975) reported polyneuropathies in approximately 50 percent of 74 patients poisoned by daily ingestion of 3.3 or 10.3 mg/day of arsenic trioxide or arsenic sulfide in antiasthmatic medicinal pills. Similarly, Silver and Wainman, (1952) reported on a patient that had ingested approximately 8.8 mg of arsenic trioxide daily for 28 months as an asthma treatment. Signs of peripheral neuropathy appeared at about two years, well after the onset of other arsenic-related effects, e.g., skin changes; assuming regular ingestion of the arsenical each day for two years, then, the neuropathy appear to be associated with gradual exposure to a maximum total dose of up to 650 mg of arsenic. Comparison of this estimate (650 mg) with that from the Mizuta, et al. (1956) study (60 mg) suggests marked variation in individual susceptibility to neurotoxic effects of arsenic resulting in frank clinical neuropathies.

The above studies characterizing clinically-manifest peripheral neuro pathies with relatively high acute, subacute, or chonic exposure, have raised questions as to whether similar but subtle neurotoxic effects are induced by chronic exposure to lower levels of arsenic. Takahashi (1974), for example, reported that abnormal electromyograms (EMG) were found in the absence of subjective symptoms among population groups living in the vicinity of an arsenic mine and smelter in Japan.

Few other epidemiology studies have attempted to delineate more precisely qualitative or quantitative relationships between chronic arsenic exposure and the induction of peripheral neurotoxic effects indexed by EMG or NCV recordings and neurologic examinations. Landau, et al. (1977) reported relationships between length and intensity of occupational arsenic exposure (mainly to arsenic trioxide via inhalation) of smalter workers and alterations in peripheral nerve functioning. The manner in which the data were reported, however, precludes precise characterization of dose-effect/dose-response relationships. Similar difficulties exist in terms of attempting to characterize such relationships for arsenic-induced peripheral nerve deficits demonstrated by EMG recording in studies of two other chronically exposed populations: (1) an Indian population exposed partly via occupational contact with arsenic in a gold mining and smelting facility in Yellow Knife, Canada, or via arsenic emissions from the facility into the ambient environment (Canadian Public Health Assoc., 1978); and (2) a Nova Scotia population exposed via geologically natural arsenic contamination of wells used for drinking water (Hindmarch, et al. 1977).

Several of the clinical reports dicussed above not only document peripheral nerve damage induced by exposure to arsenic, but also contain descriptions of arsenic-induced central nervous system (CNS) disturbances or encephalopathic effects ranging in severity from memory losses and general mental confusion to convulsions, stupor, coma, and even death (e.g., Heyman, et al. 1956; Jenkins, 1966; Frank, 1976; Nagamatsu and Igata, 1975; O'Shaughnessy and Kraft, 1976; Garb and Hine, 1977). The onset and courses of such CNS effects have not been well defined, but appear to parallel rather closely the development of peripheral neuropathy; and cases of prolonged encephalopathy indexed by electroencephalogram (EEG) recordings of abnormal brain wave patterns up to a year after cessation of exposure have been reported (Freeman and Couch, 1978; Bental, et al. 1961). Very little information regarding dose-effect/dose-response relationships for arsenicinduction of CNS effects can be derived from these studies, however, and such effects appear to be a much less constant feature of arsenic-induced neurotoxic effects in adults than are peripheral neuropathies.

Certain studies suggest, in contrast, that children may be more susceptible to arsenic-induced CNS damage. Severe CNS deficits were observed in children exposed for several months as babies to arsenic-contaminated powdered milk formulas in Morinaga, Japan (Hamamoto, 1955; Okamura, et al. 1956b; Yamashita, et al. 1972; Masahiki and Hideyasau, 1973; Japanese Pediatric Society, 1973). Follow-up studies on the children exposed to arsenic as infants have revealed: (1) increased incidence of severe hearing loss (>30 dB) in 18 percent of 415 children examined, compared to less than 1 percent incidence of hearing loss in corresponding age group children; (2) increased incidence of abnormal electroencephalographic (EEG) brain wave patterns in 14 percent of the exposed children, more than double the expected rate for comparable normal pediatric populations; and (3) observations of increased incidences of persisting mental retardation, epilepsy, and other indications of severe brain damage. In additon, Ohira and Aoyama (1972) reported not only increased EEG abnormalities but also visual system damage, including pathological eye changes, in children fed the arsenic contaminated powdered milk in comparison to nonexposed breast-fed infants. Taking into account known information regarding length of exposure and dose levels, it can be calculated that the above persisting (probably permanent) types of CNS damage effects resulted from ingestion of approximately 3.5 mg/day of arsenic resulting in a total intake of about 90-140 mg.

In another study (Bencko and Syman, 1970), hearing losses in children were reported to be associated with arsenic exposure derived from emissions from a nearby power plant combusting high-arsenic content coal. Both air and bone conduction hearing losses were observed, suggesting inner ear damage. Failure to find analogous hearing losses in children exposed to atmospheric arsenic emitted from a nearby copper smelter in the United States (Milham, 1977) has raised questions regrading arsenic-induced damage to the inner ear in children. Evidence supportive of the possible occurrence of such effects has been obtained in an animal toxicology study (Aly, et al. 1975) that demonstrated hearing losses and histopathological confirmations of destruction of the organ of Corti and other inner ear damage in guinea pigs exposed to arsenic over a two-month period via intraperitoneal (i.p.) injections of sodium arsenate solutions at a dosage level of 0.2 mg/kg body weight.

Very few animal toxicology studies have focused on investigation of neurotoxic effects of arsenic on the CNS. Rozenshstein (1970), for example, reported evidence of CNS functional deficits, as indexed by altered conditioned reflexes, as well as histopathologic evidence of CNS structural damage, e.g., pericellular edema and neuronal cytolysis in the brain, in rats exposed for three months to an arsenic trioxide aerosol resulting in an arsenic concentration of 46 $\mu g/m^3$. Similar but less severe effects were also obtained with exposure of other rats to a 3.7 μg As/m^3 aerosol. CNS deficits, indexed by impaired avoidance conditioning in the absence of demonstrable histopatholotic changes in brain tissue, were also reported (Osata, 1977) for suckling rats administered 2 or 10 mg arsenic trioxide via stomach intubation over a 40 day period.

Synergism and/or Antagonism

Moxon (1938) first demonstrated the protective effect of arsenic against selenium poisoning when he found that arsenic at 5,000 $\mu g/l$ as sodium asenite in the drinking water largely prevented liver damage in rats whose diet contained selenium at 15 μg/g as seleniferous wheat. Moxon and Dubois (1939) then showed that arsenic was unique in its ability to prevent selenium toxicity; all other elements studied were unable to protect against all manifestations of chronic selenosis. Sodium arsenite and sodium arsenate were equally effective against seleniferous grain, but the arsenic sulfides were ineffective (Dubois, et al. 1940). Arsanilic acid and 3-nitro-4-hydroxyphenylarsonic acid, two organic arsenicals used as "growth-promoters" for livestock, also exhibited a beneficial action against selenium poisoning in rats when given in the drinking water (Hendrick, et al. 1953). There is evidence that it would be practical to use these two agents to protect swine and poultry in high-selenium regions (Carlson, et al. 1954; Wahlstrom, et al. 1955). Amor and Pringle (1945) even suggested the use of an arsenic-containing tonic as a prophylactic agent against selenium poisoning in exposed industrial workers.

The metabolic basis for the beneficial effect of arsenic in selenium poisoning remained confused for some time, because arsenic was known to block the biosynthesis of dimethylselenide, a detoxification product in animals that received subacute doses of selenium by injection (Olson, et al. 1963). Moreover, the protective effect of arsenic against dietary selenium was not seen if the arsenic was given in the diet, instead of the drinking water (Ganther and Baumann, 1962a). Frost (1967) has shown that the toxicities of arsenic and selenium are additive if both elements are given in the drinking water. These results agree with those of Obermeyer, et al. (1971) who recently observed an additive toxicity between arsenite and trimethylselenonium chloride or dimethylselenide.

Ganther and Baumann (1962) studied the influence of arsenic on the metabolism of selenium when both elements are injected in subacute doses and found that the excretion of selenium into the gastrointestinal tract was markedly stimulated by arsenic. Levander and Baumann (1966a) observed an inverse relationship in arsenic-treated rats between the amount of selenium retained in the liver and the amount excreted into the gut; and they concluded that the bile might be the route by which selenium was appearing in the gastrointestinal tract. This hypothesis proved correct when it was discovered that in three hours over 40 percent of the selenium injected could be recovered in the bile of rats that also received arsenic, whereas only 4 percent of the selenium was excreted into the bile of rats not given arsenic (Levander and Baumann, 1966b). This effect of arsenic on the biliary excretion of selenium was not confined to subacute toxicity experiments: a response of selenium to arsenic was seen at doses approaching a rat's daily intake of selenium when fed some crude commercial diets. Sodium arsenite was the most effective form of arsenic in enhancing the biliary excretion of selenium, but arsenate and 3-nitro-4-hydroxylarsonate were also active to some extent. In experiments with radioactive arsenic, it was found that selenium stimulated the biliary excretion of arsenic, just as arsenic stimulated the excretion of selenium. Initial attempts to characterize the forms of selenium in rat bile suggested that the element is probably present in several forms, including some macromolecularly bound selenium.

Although these studies provide physiologic information concerning the interaction of arsenic and selenium, the chemical mechanism of the process is still far from clear. The most logical hypothesis to account for the arsenic-selenium antagonism from the molecular point of view assumes that arsenic combines with selenium--perhaps, in analogy with sulfur chemistry, by reacting with selenol (-SeH) groups to form a detoxification conjugate that passes readily into the bile (NAS, 1977a).

Teratogenicity

Although few human epidemiologic studies have provided evidence of arsenic-induced reproductive or teratogenic effects, several studies have shown that sodium arsenate induces developmental malformations in a variety of test animals: embryo chick, hamster, rat, and mouse (Ancel, 1946; Ridgeway and Karnovsky, 1952; Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974).

Pregnant golden hamsters injected with sodium arsenate (15 to 25 mg/kg body weight) produced offspring with a range of developmental malformations including anencephaly, renal agenesis, rib malformation, cleft lip and palate, and anophthalmia. The percentages of living embryos with various selected malformations following maternal treatment with 20 mg/kg sodium arsenate on the 8th day of gestation were as follows: nearly 90 percent with all malformations; over 80 percent with anencephaly; nearly 70 percent with rib malformations; and 30 percent with exencephaly. The spectrum of malformations varied with the time of injection during critical stages of embryogenesis. Malformations induced by arsenate differed from those induced by other teratogenic agents including certain heavy metals (Ferm, et al. 1971).

In another study, single intraperitoneal injections of sodium arsenate (45 mg/kg) in Swiss-Webster mice between the 6th and 11th days of gestation consistently caused an increase in fetal resorptions, a significant decrease ($p \leq 0.05$) in fetal weights compared to controls, and a number of fetal malformations, most frequently the following: exencephaly, shortening of the jaws with consequent protrusion of the tongue, exophthalmos, missing pinna, cleft lip, hydrocephalus, umbilical hernia, ectrodactyly, micromelia, and shortened or twisted tail or limb, or both. Malformations were dependent on the stage of embryogenesis. Exencephaly occurred in 54 percent of the fetuses when the injection was administered on day 9 of gestation; fusion of the ribs occurred in 100 percent of the fetuses when the injection was given on day 9; and fusion of the vertebrae occurred in 73 percent when the injection was given on day 10 (Hood and Bishop, 1972).

In a later report, Ferm (1977) demonstrated that administration of 20 mg/kg of sodium arsenate intravenously or intraperitoneally to golden hamsters during days 8 to 9 of gestation induced a specific spectrum of malformations including exencephaly, encephaloceles, skeletal defects, and malformations of the genitourinary system. The last effect, which appears to be unique to arsenate, occurred in both sexes and with high frequency.

Ferm (1977) further showed that radioactive arsenic (^{74}As) injected intravenously into Golden hamsters on day 8 of gestation was transmitted across the placenta during the critical stage of embryogenesis and appeared in the fetal tissues. Ferm (1977) refers to a report concerning a case of arsenic trioxide poisoning during human pregnancy, which demonstrated the "ease with which inorganic arsenic crosses the human placenta at term with extremely high levels in the fetal liver, brain, and kidneys" (Ferm, 1977). Introduction of arsenic into fertilized bird eggs has led to malformations of beak and brain (Peterkova and Puzanova, 1976).

Hood, et al. (1977) compared the prenatal effects of oral and intraperitoneal administration of sodium arsenate in mice. Intraperitoneal administration had a considerably greater effect than oral administration on prenatal mortality, reduction of fetal weights, and occurrence of fetal malformations. The dosages were 40 mg/kg (intraperitoneal) and 120 mg/kg (oral).

Hood, et al. (1977) further noted that although arsenite is considerably more toxic than arsenate, it has received less attention from teratologists. Intraperitoneal injection of mice in utero with 10 to 12 mg/kg arsenate on one of days 7 to 12 of pregnancy caused significant increases in prenatal mortality ($p \leq 0.05$), and daily treatment on days 8, 9, and 10 resulted in gross and skeletal malformations similar to but less frequent than those induced by comparably toxic levels of arsenate (Hood, et al. 1977).

In another study, Tamura (1978) found no effects on growth and development of rats fed arsenic trioxide from the 7th to the 21st day postnatally at a dose level of 1.5 mg/kg/day in comparison to a 50 percent mortality rate at a 15 mg/kg dose.

Mutagenicity

Most mutagenesis research has centered on chromosomal reactions to sodium arsenate. There are no data based on the host-mediated assay or the dominant lethal technique (NAS, 1977a).

One of the earliest observations that has meaning today was made by Levan (1945). Root meristem cultures of Allium cepa were treated for 4 hours with an unspecified arsenic salt at 10 concentrations, from lethal to a no-effect. Chromosomal changes were observed, including spindle disturbances and metaphase arrests. Similar effects, with minor variations, were observed after treatment with salts of 24 other metals (mostly nitrates). The changes resembled those caused by colchicine, but they cannot be considered serious damage (NAS, 1977a).

Petres and Hundeiker (1968) and Petres, et al. (1970, 1972) have reported chromosomal breakage in human leukocyte cultures after short-term in vitro exposure to sodium arsenate and in cultures obtained after long-term exposure to arsenical compounds in vivo.

The cytotoxic and mutagenic effects of sodium arsenate were tested in vitro on phytohemagglutinin-stimulated lymphocyte cultures at concentrations of 0.05-30 μg/ml of culture medium (Petres, et al. 1970). It was reported that 33 percent of metaphase plates were pulverized at 0.1 μg/ml and 80-100 percent at concentrations of 2 μg/ml or greater. The "mitosis index" and the "(^{3}H)thymidine-labeling index" were decreased. Arsenate has also been found to increase the total frequency of exchange chromosomes in Drosophila melanogaster treated with selenocystine, (Walker and Bradley, 1969). The overall significance of these chromosomal studies is difficult to assess, inasmuch as many unrelated compounds may cause similar effects. The fact that arsenic compounds have caused chromosomal damage in a number of biologic systems, however, should alert toxicologists to a possible role of arsenic in chemically-induced mutagenesis (NAS, 1977a).

In vivo studies were made on 34 patients at the University of Freiburg Skin Clinic (Petres, et al. 1970). Thirteen of these patients had recieved intensive therapy, some more than 20 years before the experiment; most of these were psoriasis patients. The control group (21 patients) consisted of 14 psoriasis patients and seven with eczema, none of whom had had arsenic treatment. Phytohemagglutinin-stimulated lymphocyte cultures were prepared from each patient for evaluation of chromosomal aberrations. The incidence of aberrations was remarkedly greater in the cultures of patients who had been treated with arsenic. Expressed as the frequency per 1,000 mitoses, 49 secondary constrictions occurred in the arsenic group and 12 in the control; gaps were found in 51 in the arsenic group and seven in the control; 26 "other" lessions occurred in the arsenic group and one in the control; and broken chromosomes appeared at the rate of 65 per 1,000 mitoses in the arsenic group and two in the control. Aneuploidy was found at the expected frequency in the arsenic group. The extent of abnormalities attributed to treatment with arsenicals is impressive; it is important that this study be repeated (NAS, 1977a).

The occurrence of chromosome aberrations was studied by Beckman, et al. (1977) in short-term cultured leukocytes from mine workers exposed to arsenic at the Ronnskar smelter in northern Sweden. In the smelter workers, 87 aberrations were found in 819 mitoses (Table 7). The number of aberrations

TABLE 7

Chromosome Aberrations in Workers Exposed to Arsenic from Ronnskar, Sweden and Controls*

	Arsenic Workers	Controls
No. of cells	819	1,012
No. of aberrant cells	71	13
No. of aberrations		
Gaps	56	9
Chromatid aberrations	12	3
Chromosome aberrations	19	1
Total	87	13
No. of aberrations per cell	0.1062	0.0128
Frequency of aberrant cells, %	8.7	1.3

*Source: Beckman, et al. 1977

TABLE 8

ancer, by Site*

increased from 0 to 25 aberrations per 100 cells. In the control material 10 aberrations were found by these investigators in 1,012 mitoses. Thus, it was found that the frequency of aberrations was significantly higher ($p \leq 0.001$) among the arsenic-exposed workers. The three types of aberrations observed in this study, gaps ($p \leq 0.001$), chromatid aberrations ($p \leq 0.01$), and chromosome aberrations ($p \leq 0.001$) were significantly increased.

Paton and Allison (1972) investigated the effect of sodium arsenate, sodium arsenite, and acetylarsan on chromosomes in cultures of human leukocytes and diploid fibroblasts. Subtoxic dose of the arsenicals were added to leukocyte and fibroblast cultures at various times between 2 and 48 hours before fixation. In leukocyte cultures treated with sodium arsenate at $0.29\text{-}1.8 \times 10^{-8}M$ for the last 48 hours of the culture period, 60 percent of 148 metaphases examined were found to have chromatid breaks. No significant breaks were found in cultures treated with sodium arsenate at $0.58 \times 10^{-8}M$, the highest nontoxic concentration. However, treatment with acetylarsan at $6.0 \times 10^{-8}M$ resulted in 20 percent chromatid breaks in 50 metaphases examined. Sodium arsenate caused chromosomal damage in diploid fibroblasts to which sodium arsenite ($0.29\text{-}5.8 \times 10^{-8}M$) was added to the medium for the last 24 hours of culture; chromatid breaks were found in 20 percent of 459 metaphases examined. These results supported the *in vitro* observations of Petres, et al. (1972) and Petres and Hundeiker (1968).

Carcinogenicity

The case for the association of inorganic arsenic with skin and lung cancer, as well as other visceral carcinomas, has been extensively reviewed (IARC, 1973; NIOSH, 1975; Hernberg, 1977; and others). The most salient points concerning pertinent literature and reviews are evaluated below.

The clinical association of skin cancer with the oral administration of arsenic compounds began with a report by Hutchinson (1888). He described six patients in whom skin cancer occurred and who had suffered for very long periods from diseases of the skin (five with psoriasis, one with pemphigus) typified by multiple lesions. Multiple lesions occurred even when squamous cancers arose in keratoses; there was an average of two lesions per case.

The elapsed time from the beginning of administration of the arsenical drug to the beginning of the epitheliomatous growth was variable, but averaged 18 years, regardless of the type of lesion. In cases with keratosis, the latent period to the onset of keratosis was about half the latent period to the onset of the epithelioma, i.e., about 9 years. In spite of the long induction period, arsenic-related skin cancers started when the patients were relatively young, 33 percent when they were 40 or younger, and 70 percent when they were 50 or younger.

Of the 143 patients, 13 had or developed miscellaneous cancers at other sites, but such cases were not reported systematically; the reports commonly presented one or a few case histories. For example, Regelson, et al. (1968) reported a case of hemangioendothelial sarcoma of the liver in a 49-year-old man who had taken Fowler's solution intermittently for 17 years to control psoriasis.

There have been numerous reports of arsenic-induced occupational cancer, such as those of the excess lung-cancer mortality among Southern Rhodesian miners of gold-bearing ores containing large amounts of arsenic (Osburn, 1957), and of the occurrence of lung and liver cancer and clinical arsenism among German vineyard workers exposed to arsenic-containing insecticides (Braun, 1958; Roth, 1957, 1958). The association of cancer with a high degree of arsenic exposure has often been based on the existence of palmar and plantar keratoses (Sommers and McManus, 1953). However, because of the increased concentration of arsenic in the lesions of Bowen's disease, arsenic has been considered as a possible cause of the disease and accompanying visceral tumors (Graham, et al. 1961), without overt prior exposure to arsenicals.

A number of relatively quantitative studies of cancer attributable to occupational exposure to arsenicals exists as discussed in this document.

A death-record examination was made of a British plant that manufactured sodium arsenite sheep dip (Hill and Faning, 1948; Perry, et al. 1948). The factory was in a small country town within a specific birth and death registration subdistrict. In this and adjacent subdistricts, death certificates of 75 workers and 1,216 men (not factory workers) in three other occupational groups were obtained for the period 1910-1943. Of the 75 deaths among factory workers, 22 (29 percent) were due to cancer; of the other 1,216 deaths, 157 (13 percent) were due to cancer. The proportion of deaths due to cancer was even higher among men who actually worked with the manufacture and packaging of the arsenic-containing material: 16 of the 31 deaths of men so classified were due to cancer. The number of deaths due to cancer according to site for the two groups is shown in Table 8, in which those deaths are expressed as a fraction of cancer deaths and as a fraction of total deaths. The absolute numbers of deaths and the fraction of cancer deaths are from the author's paper; the fractions of total deaths were calculated for this report. The data suggest a relative excess in the factory workers of cancers of the respiratory system and skin, whether calculated on the basis of cancer deaths or of total deaths; the corresponding deficits in cancers of the digestive organs and peritoneum disappear when calculated on the basis of total deaths.

TABLE 8

Death Due to Cancer, by Site*

	No. Cancer Deaths		Fraction of Cancer Deaths, %[a]		Fraction of Total Deaths, %[a]	
	Factory Workers	Other 3 Occupational Groups	Factory Workers	Other 3 Occupational Groups	Factory Workers	Other 3 Occupational Groups
Buccal cavity and pharynx	2	10	9.1	6.4	2.7	0.8
Digestive organs and peritoneum	5	91	22.7	58.0	6.7	7.5
Respiratory organs	7	25	31.8	15.9	9.3	2.1
Genitourinary	2	13	9.1	8.3	2.7	1.1
Skin	3	2	13.6	1.3	4.0	0.2
Other or unspecified	3	16	13.6	10.2	4.0	1.3
Total	22	157	99.9	100.1	29.4	13.0

*Source: Hill and Faning, 1948

[a] There were 75 deaths among the factory workers and 1,216 deaths in the other three occupational groups (see text).

Although Hill and Faning (1948) stated that the numbers of cancer deaths are small, they concluded that "there is a suggestion in the figures that the factory workers have been especially affected in the lung and skin." Hence, there was an investigation of the environmental conditions at the factory and the clinical condition of the workers in question, compared with employees in other branches of the factory who were not exposed to arsenic (Perry, et al. 1948). The median air arsenic content for the chemical workers at the various operations ranged from 254 to 696 $\mu g/m^3$. As an upper limit, this was stated to represent the inhalation of about 1 g of arsenic per year. This amount of arsenic is roughly equivalent to the amount received by patients using arsenic medication for skin diseases.

The excretion of arsenic in the urine of 127 current employees was determined; the scatter of these values was very wide. Some exposed workers excreted from 1 to nearly 2 mg/day, whereas many excreted less than 100 µg/day. A few of the persons in the control group had very high excretion rates, for which the authors found no explanation. It is important to note that 20 of the 31 factory workers had been exposed to airborne sodium arsenite for more than 20 years, and five of them for 40-50 years. Furthermore, the median age of the 31 exposed workers was 52 years, and the average age was 50. None of these men's lungs had pathologic signs attributable to their exposure to sodium arsenite (radiographs were made, and vital capacity and exercise capacity were measured).

The mortality experience of 8,047 white male smelter workers exposed to arsenic trioxide during 1938-1963 was compared by Lee and Fraumani (1969) with that of the white male population in the same state. There was a threefold excess total mortality from respiratory cancer in smelter workers, and this reached an eightfold excess for employees working more than 15 years and heavily exposed to arsenic. When respiratory cancer deaths were grouped according to degree of arsenic exposure, the observed mortality was significantly higher than expected in all three groups: approximately 6.7, 4.8, and 2.4 times the expected mortality in the heavy-, medium-, and light-exposure groups, respectively. In addition to arsenic trioxide dust, smelter workers were concurrently exposed to sulfur dioxide. Exposure to silica and ferromanganese and lead dusts occurred in parts of the refineries where arsenic concentrations were low. Therefore, a similar classification was made for relative sulfur dioxide exposure. Respiratory-cancer mortality was directly related to sulfur dioxide exposure, with observed deaths ranging from 6.0 down to 2.6 times the expected in heavy-, medium-, and light-exposure groups. Most work areas having heavy arsenic exposure were also medium-sulfur dioxide areas, and all jobs with heavy sulfur dioxide exposure were medium-arsenic areas. It was observed that workers with the heaviest exposure to arsenic and moderate or heaviest exposure to sulfur dioxide were most likely to die of respiratory cancer (Lee and Fraumeni, 1969).

A study by Pinto and Bennett (1963) involved a smelting plant in the state of Washington that produced arsenic trioxide as a by-product. The plant had an average employment of 904 during the years 1946-1960. During that period, a total of 229 deaths were reported among active plant employees and pensioners. Thirty-eight of the dead were classified as exposed to arsenic. Of the 38 dead employees exposed to arsenic, six died of cancer, including three cases of cancer of the respiratory tract. The total cancer experience of the arsenic-exposed workers was not higher than that of the unexposed, although there was twice as much respiratory cancer in both exposed and unexposed smelter workers as expected from male mortality experience in Washington. Mortality among workers at the same plant was restudied by Milham and Strong (1974). They criticized the methods of the Pinto and Bennett study. The records of workers from the same plant revealed 40 deaths from lung cancer, which was significantly higher than the 18 expected on the basis of rates in the general U.S. population. Recent data on mortality experience of arsenic exposed workers by Pinto, et al. (1977) is presented in Table 9.

Snegireff and Lombard (1951) made a statistical study of cancer mortality in a metallurgic plant (A) in which arsenic was handled and in a control plant (Z) in which "working conditions approximate those of Plant A except that no arsenic is handled." From 1922 to 1949, there were 146 deaths among the employees of Plant A who handled large quantities of arsenic trioxide. Of these deaths, 18 were due to cancer, including seven cases of cancer of the respiratory system. In the control plant, 12 of 109 deaths between 1941 and 1949 were due to cancer, including six due to lung cancer. The authors stated that total cancer mortality in the two plants was not significantly different from the figures for the state as a whole, and they concluded that handling of arsenic trioxide in the industry studied does not produce a significant change in cancer mortality of the plant employees. However, as pointed out by the National Institute for Occupational Safety and Health (NIOSH, 1975), there are a number of deficiencies in the report. Specifically, reanalyses of the data have revealed that actually there was a large excess (approximately fivefold) of lung-cancer deaths relative to mortality from all causes among workers in both plants. Thus, the data demonstrated evidence of a carcinogen for the respiratory system among the workers of both the plant in which arsenic trioxide was handled and the control plant.

Findings of increased risk of lung cancer among copper-smelter workers are not limited to the United States. A retrospective study by Kuratsune, et al. (1974) in Japan revealed that, of 19 males who died of lung cancer in

TABLE 9

Observed Deaths and Standardized Mortality Ratios (SMR) at Ages 65 and Over for the Period January 1,1949, through December 31, 1973, among 530 Men Retiring from the Tacoma Smelter by Cause of Death and Arsenic Exposure Index at Retirement[a,b]

Cause of Death	Total		Arsenic Exposure Index[c]									
			Under 3,000		3,000-5,999		6,000-8,999		9,000-11,999		12,000+	
	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
All causes	324	112.2[d]	87	98.1	124	110.3	70	129.2[d]	24	117.7	17	130.0
Cancer (140-205)	69	148.9[d]	15	107.9	28	156.0[d]	14	151.6	7	218.7	5	217.2
Digestive (150-159)	20	122.0	6	121.2	9	140.4	2	62.7	3	264.7	0	0.0
Respiratory (160-164)	32	304.8[d]	5	165.6	11	279.4[d]	7	306.9[d]	4	568.5[d]	5	810.5[d]
Lymphatic (200-203, 205)	2	95.2	1	166.1	1	126.1	0	0.0	0	0.0	0	0.0
Urinary (180,181)	3	90.9										
Other cancer	12	84.5	3	56.3	7	102.8	5	150.4	0	0.0	0	0.0
Stroke (330-334)	43	113.2	18	150.3	12	80.0	7	104.5	6	218.4	1	64.7
Heart disease (400-443)	144	108.8	33	81.4	63	122.4	36	144.2[d]	5	53.6	5	83.2
Coronary (420)	120	108.9	25	74.9	52	122.2	31	145.1[d]	4	51.7	5	95.5
Other heart disease	24	108.6	8	111.5	11	123.2	5	138.4	1	62.9	0	0.0
Respiratory disease (480-493, 500-502)	11	101.8	4	116.8	3	70.9	1	52.4	2	250.8	0	0.0
All other causes	57	92.2	17	89.2	18	74.8	12	104.1	4	91.3	6	212.4

[a] Source: Pinto, et al. 1977

[b] Expected deaths were estimated on the basis of Washington State experience, 1949-1970. Includes four men with unknown exposures.

[c] Arsenic exposure index derived from Bartjer, et al.

[d] Statistically significant ($p \leq 0.05$).

a particular town, 11 had been employed as smelter workers in a local copper refinery, and in all cases the disease had become manifest after the men had stopped working at the refinery. The author's conclusion was that prolonged exposure to arsenic, and possibly also other compounds, seemed to be associated with cancer of the lungs. Additional groups exposed to inorganic arsenic such as gold miners in Rhodesia (Osburn, 1969), hard-rock miners in the United States (Wagoner, et al. 1963), and nickel refinery workers (Rockstroh, 1959) have shown an increased mortality from lung cancer, but evaluation of the role of arsenic is difficult because of the presence of other carcinogens in the working atmosphere.

A study at the Dow Chemical Company examined the incidence of respiratory cancer among 173 descendents who were exposed primarily to lead arsenate and calcium arsenate and 1,809 descendents who worked in the same plant and were not exposed to those compounds (Ott, et al. 1974). Data were presented on the relationship between cumulative arsenic exposure and the ratio of observed to expected deaths from lung cancer. The average exposure of each worker was calculated on the basis of records of job assignments and data on the arsenic content of the air in various parts of the plant. Deaths from respiratory malignancy were seven times greater than expected for total inhaled quantitites of 29.8 g and 2-4 times greater for 0.13-6.56 g. There was no association between the extent of exposure and the time from beginning of exposure to death; most of the respiratory cancers occurred 20-40 years after initial exposure, regardless of total exposure.

The ratio of observed to expected deaths was even higher (3.85:1) in another category, malignant neoplasms of the lymphatic and hematopoietic tissues except leukemia, than it was in malignant neoplasms of the respiratory system (3.45:1). Six lymphomas were reported, with the following diagnoses on the death certificates: four cases of Hodgkin's disease, one of lymphoblastoma, and one of reticulum cell sarcoma.

By contrast with the Dow Chemical Company workers, orchard workers who sprayed lead arsenate were reported as showing no evidence of increased cancer (Nelson, et al. 1973). A mortality study involving a cohort of 1,231 morbidity survey of the effects of exposure to lead arsenate insecticide spray was conducted in 1968-1969. Air concentrations of arsenic during spraying averaged 0.14 mg/m^3. The population was grouped according to exposure in three categories and compared in terms of standardized mortality ratios with the mortality experience of the state of Washington. There was no evidence of increased mortality from cancer, heart disease, or vascular lesions.

In 1974, the mortality experience of retired employees of an Allied Chemical Company pesticide plant in Baltimore was analyzed (Baetjer, et al. 1975; NAS, 1977a). The employees had been exposed to a number of industrial chemicals, including arsenicals; there were no data on the extent of exposure to the various chemicals. Incidence of death among the retirees was 3.5 times that among the general Baltimore population. The excess mortality was concentrated in cancer-caused deaths (14 times the expected), particularly respiratory cancer and lymphatic cancer. The noncancer deaths were at the expected rates. These calculations were based on a total of 22 deaths in men from all causes during the period 1960-1972.

Several human studies not generally available were reviewed in the National Institute of Occupational Safety and Health document on occupational exposure to inorganic arsenic (NIOSH, 1975), including unpublished reports to Kenncott Copper Corporation in 1971 and 1974; unpublished papers presented at the Conference on Occupational Carcinogenesis in New York City on

March 24-27, 1975; and an evaluation by NIOSH of the study by Nelson, et al. (1973). In the latter case, independent sources of information investigated by NIOSH contradicted, rather than confirmed, the report by Nelson, et al. (1973). The conclusion drawn was that the report apparently did not accurately depict the cancer incidence of persons exposed to lead arsenate spray in the Wenatchee Valley (NIOSH, 1975).

High incidences of skin cancer have been reported in several population groups exposed to high concentrations of arsenic in drinking water, including people in the district of Reichenstein in Silesia, (Geyer, 1898), Cordoba Province in Argentina, (Bergoglio, 1964), and Taiwan (Tseng, et al. 1968).

Chronic arsenical poisoning, including skin cancer and a gangrenous condition of the hands and feet called Blackfoot's disease, has occurred in several communities exposed to arsenic in drinking water. The best documented instance of such arsenical poisoning is in Taiwan (Yeh, et al. 1968; Yeh, 1963, 1973; Tseng, et al. 1968; Tseng, 1977). In a house-to-house survey of 40,421 people in 37 villages along the southwest coast of Taiwan, Tseng, et al. (1968) found that the prevalence of skin cancer, hyperpigmentation, and keratosis each correlated with the arsenic content of the water. The highest range of concentrations was greater than 0.6 ppm, and the lowest range was less than 0.29 ppm. From a general survey of these inhabitants, the prevalence rate for arsenical skin cancer was 10.6 per 1,000 residents in 1965. The skin cancer rate for well water containing ≤ 0.60 ppm was 21.4 per 1,000 people, while at <0.29 ppm it was 2.6 (Tables 10 and 11; Figures 1, 2, and 3).

The sources of drinking water for these areas were deep artesian wells, used from around 1910 until 1966, when a tap water supply was installed.

TABLE 10

Age-specific and Sex-specific Prevalence Rate for Skin Cancer*

	Male		Female		Total	
Age	Per 1,000	Number	Per 1,000	Number	Per 1,000	Number
0-19	--	0	--	0	--	0
20-29	1.0	2	1.1	3	1.1	5
30-39	9.7	20	1.5	4	5.0	24
40-49	25.9	40	8.0	16	15.7	56
50-59	80.8	99	28.9	38	53.7	137
60-60	124.8	92	57.0	40	91.9	132
70+	209.6	57	53.8	17	125.6	74
Total	16.1	310	5.6	118	10.6	428

*Source: Tseng, 1977

TABLE 11

Causes of Death in Patients with Skin Cancer and Patients with Blackfoot Disease*

Cause of Death	Skin Cancer Patients		Blackfoot Disease Patients		General Population in Endemic Area	
	No.	%	No.	%	No.	%
Cancer	68	27.9	99	18.8	125	13.1
Lung	15	6.1	21	4.0	21	2.2
Skin	15	6.1	12	2.3	3	0.3
Bladder	10	4.1	17	3.2	16	1.7
Liver	6	2.5	21	4.0	17	1.8
Colon	5	2.0	3	0.6	12	1.3
Kidney	5	2.0	—	0	—	0
Stomach	3	1.2	4	0.8	13	1.4
Nasal cavity	2	0.8	5	0.9	16	1.7
Bone	2	0.8	4	0.8	2	0.2
Uterus	1	0.4	2	0.4	6	0.6
Esophagus	—	0	4	0.8	2	0.2
Miscellaneous	4	1.6	6	1.1	17	1.8
Cardiovascular disease	30	12.3	83	15.7	87	9.1
Gangrene	7	2.9	70	13.3	—	0
Cerebrovascular disease	32	13.1	63	12.0	91	9.6
Respiratory disease	46	18.9	100	18.9	231	25.1
Pulmonary tuberculosis	10	4.1	41	7.8	55	5.8
Pneumonia	17	7.0	28	5.3	117	12.3
Others	19	7.8	31	5.9	67	7.0
Disease of the alimentary tract	13	5.3	34	6.4	118	12.4
Senility	12	4.9	22	4.2	50	5.3
Renal disease	7	2.9	21	4.0	34	3.6
Miscellaneous	13	5.3	30	5.7	207	21.8
Unknown	16	6.6	6	1.1	—	0
Total	244		528		951	

*Source: Tseng, 1977

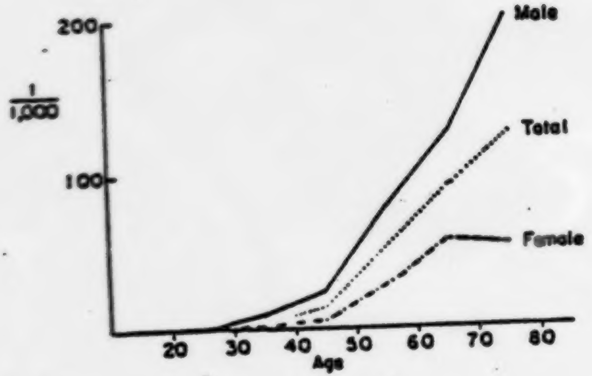

FIGURE 1

Age and Sex-specific - Prevalence Rate for Skin Cancer
Source: Adapted from Tseng, 1977.

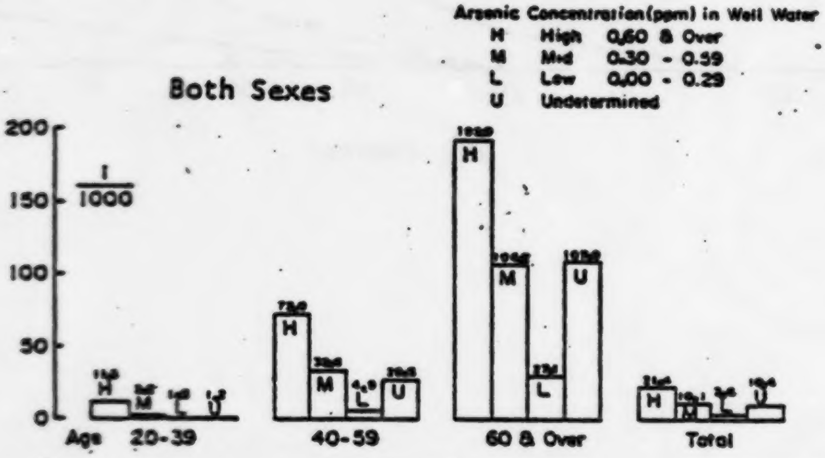

FIGURE 2

Age-specific Prevalence Rate (1/1,000) for Skin Cancer by Arsenic Concentration in Well Water

Source: Tseng, 1977

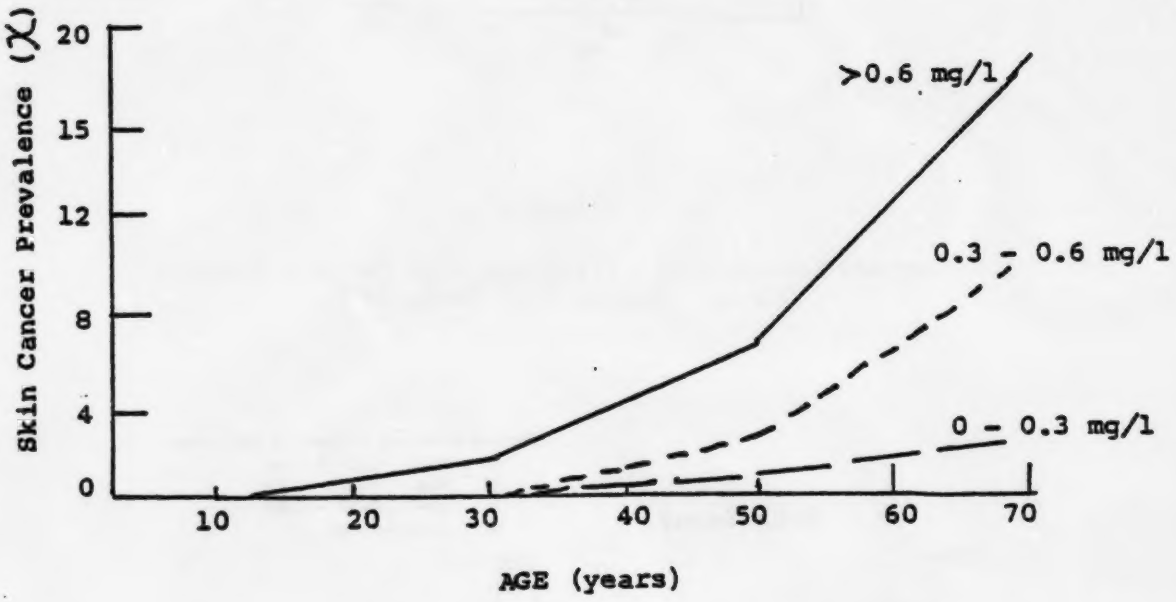

FIGURE 3

Graphical Representation of Figure 2

The concentrations of arsenic in the water ranged from 0.01 to 1.82 ppm (median range was 0.4 ± 0.6 ppm). The chemical form of arsenic in the water was not clearly determined, but it may have been either trivalent (because the well water is probably anaerobic) or a methylated arsine (because the authors observed a combustible gas, perhaps methane, bubbling from the water storage tanks). Initial attempts to measure the arsenate to arsenite ratio of the water have been confined to measurements in a United States laboratory of a sample shipped from Taiwan with no special precautions to preserve the speciation occurring at the collection point (Table 12) (Irgolic, 1979). Therefore, from the best available information, people in that region of Taiwan could have been exposed to both trivalent and pentavalent arsenic compounds.

Assessing the Taiwan situation is more complex than simply identifying the two oxidation states of arsenic, as suggested recently by Lu, et al. (1975, 1977a,b). These workers have observed nonarsenical fluorescent compounds in water samples from the areas where Blackfoot disease is endemic and have identified one of the fluorescent components as an alkaline hydrolysate of ergotamine, lysergic acid, or a related compound (Lu, et al. 1977b). They have also shown that one of the fluorescent components produced abnormalities in developing chick embryos (Lu, et al. 1977a). It is not known whether ergotamine was the compound that produced these abnormalities.

The evidence of arsenical waters in an eastern area of the province of Cordoba, Argentina, has been known for many decades and is associated with the occurrence of hyperpigmentation, keratosis, and skin cancer. A study made in 1949-1959 indicated a higher proportion of deaths from cancer in the arsenical region than in the rest of the province -- 23.8 percent versus

TABLE 12

Analysis Results for the Taiwan Water Samples*

Element	Geographic Location Pei Men	 Pu Tai
Arsenite[1], ppm As	0.05	0.09
Arsenate[1], ppm As	0.52	0.63
Arsenite and Arsenate	0.57	0.72
total As, ppm (AAS)[2]	0.72	0.76
total As, ppm (NAA)[3]	0.76	—
Sodium, ppm	282	223
Copper, ppm	<0.1	<0.1
Manganese, ppm	<0.1	<0.1
Zinc, ppm	<0.1	<0.1
Iron, ppm	<0.1	<0.1

*Source: Irgolic, 1979.

[1] Determined by GC-MES

[2] Flameless Atomic Absorption Spectrometry

[3] Neutron Activation Analysis

15.3 percent (Bergoglio, 1964). The excess was due mainly to cancer of the respiratory and digestive tracts in both men and women. The excess cancer was unrelated to socioeconomic differences.

In contrast to the above epidemiology studies yielding evidence for increased cancer rates in populations exposed to arsenic via drinking water supplies, a study conducted by Morton, et al. (1976) failed to demonstrate any increased incidence of cancer in Lane County, Oregon, the only area in the United States where the drinking water supply has elevated levels of arsenic. Several possible explanations can be offered for the lack of effects seen in Lane County in comparison to positive observations in other areas, e.g., Taiwan. These include the following:

(1) arsenic concentrations in the Lane County drinking water supply were distinctly lower than those measured in Taiwan;

(2) the predominant form of arsenic in the Taiwanese water was trivalent arsenic which tends to be more toxic than the pentavalent form found in Lane County;

(3) an insufficient number of subjects to reveal small increases in cancer rates may have been studied in the Lane County area, an area much less densely populated than Taiwan and having fewer total numbers of subjects available for study;

(4) differences in racial characteristics and nutritional status between the two experimental populations may have affected the results;

(5) the presence of other carcinogenic contaminants in the Taiwanese water but not in the Lane County water may have increased the cancer rate independent of the presence of arsenic.

While none of the above explanations can be ruled out as crucial factors, neither can the observed differences in cancer rates be conclusively attributed to any one of them.

In general, animal studies have not shown carcinogenicity for arsenic compounds, even when administered at near the maximally tolerated dosage for long periods. Certain notable exceptions are described first, and then several of the negative studies.

Askanazy (1927) noted benign and malignant teratomas in rat embryos transplanted into the peritoneal cavity of rats whose drinking water contained arsenic. Embryonal cells are especially sensitive to arsenic which provoked in them signs of degeneration even in concentrations of 0.25 µg/l of cultivation medium (Goeckerman and Wilheim, 1940).

In 1962, Halver reported the occurrence of hepatomas in trout fed a synthetic diet containing carbarsone at 4.8 mg/g of diet (the data were reviewed by Kraybill and Shimkin (1964); the original report is not readily available). Of 50 trout exposed to carbarsone, five developed hepatomas. There were no hepatomas in a large control group fed the synthetic diet without carbarsone. However, aflatoxin contamination of the diet may have been a confounding variable.

More recently, Osswald and Goerttler (1971) reported that subcutaneous injections of sodium arsenate in pregnant Swiss mice caused a considerable increase in the incidence of leukemia in both the mothers and their offspring. A 0.005 percent aqueous sodium arsenate solution was injected daily during pregnancy for a total of 20 injections, each containing arsenic at 0.5 mg/kg. Some groups of offspring from the arsenic-treated females were given an additional 20 subcutaneous injections of arsenic (0.5 mg/kg) at weekly intervals. Leukemia occurred in 11 of 24 mothers (46 percent), 7 of 34 male offspring (21 percent), 6 of 37 female offspring (16 percent), and, in the offspring given the additional 20 injections, 17 of 41 males (41 percent) and 24 of 50 females (48 percent). Leukemia developed in only 3 of 35 males (9 percent) and in none of 20 female offspring of untreated control mice. Furthermore, 11 of 19 mice (58 percent) developed lymphoma after 20 weekly intravenous injections of 0.5 mg each of arsenic as sodium arsenate.

Long-term studies of effects of arsanilic acid on chickens, pigs, and rats were reported by Frost, et al. (1962). No adverse effects were seen in the chickens and pigs after 4 years of feeding, nor in pigs fed 0.01 percent arsanilic acid for three generations. Male and female weanling rats from the F_2 generation of a six-generation breeding study in which 0.01 percent and 0.05 percent arsanilic acid was fed were held on the 0.01 percent arsanilic acid diet or on the control diet for 116 weeks. The overall tumor incidence was the same in all groups and resembled the historical incidence of tumors in the colony, 35-45 percent. The significance of these data lies in the fact that transplacental exposure to a carcinogen followed by lifetime exposure to the same carcinogen is often the most sensitive technique for detecting carcinogenicity of a substance (Tomatis and Mohr, 1973), but this test was negative.

Boutwell (1963) used female mice (Rockland and a specially bred strain highly susceptible to skin tumors) in a test for cocarcinogenicity of potassium arsenite. It was tested as an initiator, both orally by stomach tube (a total of 2.4 mg in five days) and locally (a total of 1.2 mg in eight applications during five days). This initiating treatment was followed by topical application of croton oil twice a week for 18 weeks. He also tested potassium arsenite as a promoter by daily applications (a total of 2.3 mg/week) after a single 75 μg dose of dimethylbenzanthracene (DMBA). The prolonged skin applications of potassium arsenite were hyperkeratotic and ulcerogenic. Other experiments were done to determine whether arsenic would increase the yield of skin cancers caused by a suboptimal regimen of DMBA plus croton oil given either at the time DMBA initiation or during the 24-week period of croton oil promotion. Under the latter condition, the mice were fed potassium arsenite at 169 μg/g of food. This dietary concentration of 169 μg/g (as potassium arsenite) is very high, compared with the 0.5 μg/g usually found in the human diet. In no case was there an effect of arsenite on skin carcinogenesis in these experiments. Many tumors developed in the positive control mice, beginning as early as six weeks after treatment began.

Baroni, et al. (1963) carried out a similar study with male and female Swiss mice, testing the oral effects of potassium arsenite (100 mg/l in drinking water) as an initiator with croton oil promotion and as a promoter with DMBA and urethane initiation. Local skin applications of sodium arsenate were tested as a promoter after initation with DMBA or urethane. The arsenicals had no effect on tumorigenesis; and only a very slight degree of keratosis was observed.

Milner (1969) used three strains of mice that differed in susceptibility to the induction of skin tumors by the application to the skin of methylcholanthrene-impregnated paraffin disks for 2-3 weeks. The treated site was transplanted syngenetically and observed for eight weeks for tumor formation. Arsenic trioxide (100 mg/l in drinking water) was administered either during methylcholanthrene exposure, to animals with transplanted skin, or both. Arsenic exposure produced a small increase in the yield of papillomas in the low-susceptibility strain, a small decrease in the high-susceptibility strain, and no effect in the intermediate susceptibility strain.

Byron, et al. (1967) fed either sodium arsenite or sodium arsenate to Osborne-Mendel rats in a 2-year study at dietary concentrations of 15-250 µg/g for arsenite and 30-400 µg/g arsenate. No carcinogenic activity of either material was found. These investigators also did a 2-year arsenic feeding experiment on dogs, with negative results; however, this was an inadequate observation period for studying carcinogenic responses in dogs.

Hueper and Payne (1962) incorporated arsenic trioxide in the drinking water (either plain or with 12 percent ethanol) of groups of rats and mice. The initial concentration of 4 mg/l was increased by 2 mg/l each month to a maximum of 34 mg/l at 15 months. Thus, the daily intake of arsenic trioxide ranged from 0.1 to 0.8 mg/rat. The administration of arsenic trioxide was continued until 24 months. Neither the rats nor the mice developed any cancers in suspected target organs -- skin, lung, and liver.

Kanisawa and Schroeder (1969) and Schroeder, et al. (1968) found no carcinogenic effects on mice exposed to potassium arsenite at 5 mg/l in drinking water from weaning to senescence (Kanisawa and Schroeder, 1969) or on rats on the same regimen (Schroeder, et al. 1968).

Kroes, et al. (1974) studied the carcinogenicity of lead arsenate and sodium arsenate with SPF-Wistar-derived male and female rats. In addition, some groups were intubated with a subcarcinogenic dose of diethylnitrosamine to investigate a possible synergistic action leading to lung tumors. Food intake and body weights were recorded, and complete gross and microscopic examinations were made on all animals. Lead arsenate that was incorporated in the diet at 1,850 µg/g was toxic and caused increased mortality; an adenoma of the renal cortex and a bile duct carcinoma were found in this group, but no significance can be attached to one or two tumors in any group. No cancer was associated with the feeding of lead arsenate at 463 µg/l or sodium arsenate at 416 µg/l. No synergism with the nitrosamines was observed. There was a high spontaneous-tumor incidence in this experiment. The test diets were fed to female rats from the time of parturition until the young were weaned, and these young were the test animals. Surviving rats were killed after 29 months of feeding.

As Fraumeni (1975) has pointed out, it is largely because laboratory studies have not succeeded in producing tumors in animals that arsenic has not been accepted universally as a carcinogen. There is evidence from clinical observations and occupational and population studies that inorganic arsenic is a skin carcinogen in man. There is a characteristic sequence of skin effects of chronic exposure to arsenic that involves hyperpigmentation initially, then hyperkaratosis (keratosis), and finally skin cancer (Yeh, et al. 1968). This sequence has been oserved under a variety of circumstances involving chronic exposure: potassium arsenite (Fowler's solution) was used medicinally (Neubauer, 1947), vineyard workers used sprays and/or dusting powders containing arsenic compounds and drank arsenic-contaminated wine (Braun, 1958; Roth, 1957, 1958), chemical workers manufactured sodium arsenite for use as a sheep dip (Perry, et al. 1948), and residents of a southwest area of Taiwan had, as their only source of drinking water for over 45 years, artesian wells contaminated by arsenic from geologic deposits (Tseng, et al. 1968). The similarity of responses under these diverse circumstances is important, because studies in human populations always involve variables that cannot be controlled as in laboratory experiments; hence, the credibility of information derived from human studies depends on the demonstration of comparable effects under different conditions. This requirement has been amply met regarding arsenic as a cause of skin cancer (NAS, 1977a).

The earliest skin effect of chronic arsenic exposure, hyperpigmentation (melanosis), occurs in a dappled pattern predominantly in unexposed areas. After the onset of melanosis, the skin begins to atrophy in a patchy way in hyperpigmented areas, with the formation of keratoses that are the pathogonomonic lesions of chronic arsenic exposure (Yeh, et al. 1968). Only a small proportion of the keratoses evolve into skin cancer, and this takes place only after many years. The sequence is illustrated by the Taiwan data - the prevalence of melanosis, keratosis, and skin cancer reached 10 percent in the male population roughly at ages of 18, 30, and 60 years, respectively (Tseng, et al. 1968). Chronic exposure to inorganic arsenic thus causes a slowly progressive form of patchy skin damage involving the epidermis and adnexal structures, as well as the underlying dermis, with the precancerous keratoses and cancers forming in the areas of chronic atrophy. The chronic damage and tumorigenesis resulting from arsenic are similar to the effects of ionizing and ultraviolet radiation on the skin (NAS, 1977a).

Arsenical skin cancer is readily distinguished from skin cancer induced by sunlight, in that it occurs predominantly on surfaces that are shielded from sunlight and multiple lesions are much more common in arsenic-induced cases; for example, in 428 of the 429 cases of skin cancer studied in Taiwan, there was more than one cancer (Yeh, et al. 1968).

Substantial doses of inorganic arsenic are required to produce an appreciable incidence of skin cancer. The average intake of persons treated with Fowler's solution who developed skin cancer was around 20-30 g. The prevalence of skin cancer in Taiwanese men exposed to drinking water containing arsenic at 300-600 mg/l was about 15 percent at age 60 and over. The normal incidence is 2-3 percent. On the basis of a 2 l/day water intake for the period over which the artesian wells were used (45 years), the total arsenic intake must have been about 15 g, which is roughly in the same domain as that in clinical cases of the use of Fowler's solution. Thus, the Taiwanese data that demonstrated the requirement for large doses of arsenic to obtain even a modest yield of skin cancer are consistent with the relatively low frequency of skin cancer in patients treated with Fowler's solution. The low potency of inorganic arsenic may explain why no skin effects have been reported in people treated for syphilis with organic arsenicals, inasmuch as the total doses amounted to only a few grams. However, it is also possible that the metabolism of the organic arsenicals is sufficiently different to preclude the occurrence of skin cancer and other forms of arsenical damage even at higher doses (NAS, 1977a).

The relative frequency of melanosis, keratosis, and skin cancer was roughly similar in the Taiwanese population and the chemical workers who manufactured sheep dip. On direct examination, the latter showed a 90 percent prevalence of melanosis and 30 percent prevalence of keratosis, for a ratio of melanosis to keratosis of 3:1. At comparable ages, the Taiwanese showed a ratio of about 4:1. Two of the nine keratosis patients in the sheep dip factory had already been treated for skin cancer, and the proportionality between keratosis and skin cancer was about the same in Taiwan. As in the Taiwan experience, the sheep dip chemical workers had been exposed to large doses of inorganic arsenic (up to 1 g/year), but much of this was by inhalation (NAS, 1977a).

It is possible that the trivalent and pentavalent forms of inorganic arsenic produce the same effects on skin. This is of interest, particularly in view of the different metabolic patterns of trivalent and pentavalent inorganic arsenic with the former by interaction with sulfhydryl groups and the latter by substituting for phosphate. The clinical use of Fowler's solution and the manufacture of sodium arsenite as a sheep dip both involved exposure to trivalent inorganic arsenic. The two categories of people developed similar skin responses. The Rhodesian gold miners, in whom the incidence of typical arsenical keratoses was very high, were exposed to arsenopyrite, in which the arsenic becomes trivalent on weathering; the reactions of arsanopyrite in the body are unknown (NAS, 1977a). The chemical form of arsenic in the Taiwanese artesian-well water is still being investigated, but, the reported occurrence of methane gas in the water could preclude the existence of arsenic in the pentavalent form (NAS, 1977a) and certain preliminary results by Irgolic (1979) suggest that the trivalent form of arsenic predominates. The failure to find increased incidence of cancer in Lane County, Oregon, where pentavalent, inorganic arsenic tends to predominate in water supplies lends some support to the possibility that trivalent arsenic has the greatest carcinogenic potential and is of the greatest concern.

Of the published reports on mortality from respiratory cancer in copper smelters, the most impressive is that of Lee and Fraumeni (1969). The study involved a population of 8,047 white male smelter workers who were followed for 26 years; for each employee, information was available on time, place, and duration of employment, maximal arsenic and sulfur dioxide exposures (descriptive, rather than numerical), and cause of death. The life-table method was used to evaluate age-specific mortality rates for the various causes of death, and the rates were compared with those of the states in which the smelters were. The number of deaths available for analysis was very substantial; 1,877. The study demonstrated a systematic gradient for respiratory cancer according to the magnitude and duration of exposure to both arsenic and sulfur dioxide. These agents, however, were inseparably linked, because of the nature of the smelter operations. The amount of excess cancer was impressive, with an eightfold increase in the workers who had the heaviest arsenic exposure for the longest duration, i.e., more than 15 years. The latent period -- the interval between first employment and death from respiratory cancer -- was extraordinarily long and was inversely related to the magnitude of exposure: 34, 39, and 41 years for the categories of heavy, medium, and light arsenic exposure. There were deficiencies in the study, some of which were unavoidable. For example, no indication was given of whether the study population was representative of the total workers population; the exposure rankings were based on the maximal arsenic concentrations, rather than weighted averages derived from work histories. No quantitative data were available on exposure. No attempt was made to validate the stated causes of death. No smoking histories were obtained. However, none of these deficiencies could be seriously regarded as invalidating the conclusions of the study (NAS, 1977a).

The Kuratsune, et al. (1974) report dealt with a smaller study that compared lung-cancer mortality rates calculated from the 22 deaths that occurred in a 30-year period in a smelter town with the lung cancer experience in the same period in a neighboring city and in Japan as a whole. The standardized mortality rate for males in the smelter towns was four times higher than that for the rest of the country, but equal to that for women. This 4-fold excess is comparable with the 3.3-fold excess observed in the Lee and Fraumeni (1969) study. Although many of the men in the town worked in the refinery, a much higher proportion of the lung-cancer cases, compared with controls, occurred in men who were heavily exposed to arsenic as smelter operators. As in the case of the Lee and Fraumeni (1969) study, the latent period from first exposure to the diagnosis of lung cancer was very long, ranging from 26 to 48 years. The duration of employment was also very long, with a median of about 30 years, although two cases occurred in people who worked for only 2-3 years.

Two lung cancer studies of the American Smelting and Refining Company smelter have produced conflicting results. The 1963 Pinto and Bennett report examined the proportional mortality from lung cancer in a total of 229 deaths in the period 1946-1960. This study dealt only with pensioners and workers who died during their employment and did not include people who had left the plant. The reported data showed that the 18 lung-cancer deaths in the plant population as a whole was higher than the rate in the state of Washington. However, the excess lung cancer for the plant as a whole was due to the high occurrence in controls, i.e., in workers who were considered not to have arsenic exposure. Milham and Strong (1974) by contrast, found in the years 1950-1971, that there were records of 39 deaths due to respiratory cancer in Pierce County (the smelter locale) in people who were stated to have worked at the smelter. Application of U.S. mortality rates to the published figures for the smelter population at risk yielded an expected number of 18 respiratory cancer deaths, compared with the 39 deaths observed (NAS, 1977a).

Pinto, et al. (1977) recently resolved the discrepancy between the Pinto and Bennett (1963) and Milham and Strong (1974) papers in a study of the same smelter that reevaluated the exposure categories used in the Pinto and Bennett paper (1963) (which were apparently in error) and also included a longer observation period and therefore more deaths. The data included a total of 32 respiratory cancer cases and show a progressive increase in standardized mortality ratio with increasing arsenic exposure. The arsenic-exposure index was calculated as a weighted average based on urinary arsenic concentration and duration of employment. It is of interest that the eight-fold excess in respiratory cancer for workers with the highest exposures and the threefold excess for all the smelter workers reported by Pinto et al. (1977) were very close to the figures reported by Lee and Fraumeni (1969) and Kuratsune, et al. (1974).

The studies described here indicated that excess respiratory cancer occurs in copper-smelter workers as a function of the magnitude and duration of exposure to arsenic, with latent periods of three to four decades from the time of initial exposure. However, the studies do not permit a conclusive resolution of the issue of whether concomitant exposure to sulfur dioxide and other smelter dusts is necessary for the carciogenic response. Evidence from studies involving entirely different circumstances of exposure including workers in three pesticide manufacturing plants (Hill and Faning, 1948; Ott, et al. 1974), vintners who applied pesticides (Braun, 1958), and Rhodesian gold miners (Osburn, 1969), however, suggests that sulfur dioxide and other unspecified smelter dusts are not essential cofactors for the respiratory carcinogenicity of arsenic. All the nonsmelter studies had obvious limitations, but the lung cancer excess in each study was relatively large and, taken as a group, they provide significant evidence that arsenic is a lung carcinogen (NAS, 1977a).

The Hill and Faning (1948) study of 75 deaths in a sheep dip factory used the indirect method of proportional mortality to evaluate the small group of 22 deaths from cancer; seven of them were cancers of the respiratory tract, compared with an expected 2.4 deaths. The Dow arsenic workers (Ott, et al. 1974) were evaluated in two ways: (1) by an analysis of death records of those who died from lung cancer (28, or 16.2 percent, of 173 chemical-worker deaths, compared with 104, or 5.7 percent, of the 1,809 control-case deaths), and (2) then, as a retrospective cohort study, a comparison of the mortality from respiratory cancer (obtained from the records used in the first approach) among 603 persons identified as having worked in the arsenic plant from 1940 to 1973 with the mortality among the corresponding U.S. white population. The two approaches gave essentially the same results - a threefold to fourfold excess. However, the puzzling aspect of the data is that almost 60 percent of the respiratory-cancer deaths were in people who had worked with arsenic for less than a year, three decades earlier. Most of the arsenic workers were unskilled short-term employees, of whom a large proportion left the company after a brief period of employment. The follow-up study, however, dealt only with the people who remained in the company. A confirmation of the excess lung cancer in a follow-up of short-term arsenic workers who left the company would be very useful. Nevertheless, there were about a dozen cases in people who worked longer than a year and who were in the highest dose categories, where the excess risk was maximal (fourfold to sixfold). It is possible that the apparent twofold excess in lung cancer in the lower exposure categories, including those who worked with arsenic for less than a year, would not be ascribable to arsenic, because there was no change in cancer risk over a wide range of total doses (0.04-1.56 g). Furthermore, these low dose categories consisted predominantly of short-term unskilled workers who as a group might have had higher exposures to other hazardous chemicals than the controls (NAS, 1977a).

The Allied Chemical Company pesticide manufacturing operations produced a range of products, including some arsenical compounds. A preliminary study of the proportional mortality among retired employees showed a sevenfold excess of lung cancer that accounted for about 40 percent of all deaths. Both the Dow and Allied studies also showed a few excess deaths from lymphoma and Hodgkin's disease. The results of a more detailed study of the Allied Chemical Company that is now in progress will be very useful (NAS, 1977a).

Arsenic sprays and dusts were widely used in Germany between 1925 and 1942, at which time they were banned (Braun, 1958; Roth, 1957, 1958). Vineyard workers also drank wine containing arsenic. Hundreds of workers developed acute and chronic arsenic poisoning. In the 1950's, vineyard workers with lung cancer began to appear in hospitals serving the vineyard regions. An association between arsenic and lung cancer is further suggested by the high proportion of vineyard workers with lung cancer who had the characteristic hyperpigmentation and keratoses associated with chronic arsenic exposure (NAS, 1977a).

The same high degree of association of skin arsenism and lung cancer occurred in Rhodesian gold miners who were heavily exposed to arsenopyrite dust (Osburn, 1969). In the period 1957-1963, the occurrence of 37 cases of lung cancer in gold miners represented an incidence of 206/100,000 compared with 34/100,000 for adult males in the Gwanda region of Rhodesia. This represents a sixfold difference in lung cancer in miners (NAS, 1977a).

The probability of death from lung cancer in persons with keratosis, ranges from 32 to 56 percent, which is roughly 5-10 times higher than might be expected. The data suggest that there is a very high risk of lung cancer when the exposure to inorganic arsenic dust is high enough to cause keratoses (NAS, 1977a).

The only evidence that arsenic is a liver carcinogen comes from German vintners. Thirteen of the 47 persons whose autopsies were reported by Roth (1957, 1958) had cirrhosis, and six had angiosarcoma, a rare form of liver cancer associated with exposure to vinyl chloride and Thorotrast®, and one with a duct carcinoma. Only two cases of angiosarcoma have been reported in people treated with Fowler's solution (Regelson, et al. 1968). There is no evidence of either cirrhosis or liver damage in any of the other studies on arsenic. It is possible that the combined effect of a high alcohol intake and arsenic is responsible for the unusual forms of cirrhosis and liver cancer observed in vintners. It should also be pointed out that the chemical form of arsenic in wine is unknown (NAS, 1977a).

CRITERION FORMULATION

Existing Guidelines and Standards

In 1942, the U.S. Public Health Service set a maximum allowable level of 50 µg/liter for arsenic in drinking water supplied by interstate Carrier Water Supplies. The arsenic standard remained at that level in the 1962 revision of the Drinking Water Standards and has been continued in the U.S. Environmental Protection Agency Drinking Water Standards which became effective in June of 1977.

The American Conference of Governmental and Industrial Hygienists (ACGIH, 1977) has set 0.5 mg/m^3 as the Threshold Limit Value-Time Weighted Average (TLV-TWA) for airborne arsenic. This means that the time-weighted average concentration of airborne arsenic for a normal 8-hour workday or 40-hour workweek should not exceed 0.5 mg/m^3. The Conference has issued a Notice of Intended Change (for 1977) which to reduce the TLV-TWA from 0.5 mg/m^3 to 0.05 mg/m^3 (ACGIH, 1977).

The National Institute of Occupational Safety and Health has recommended a ceiling level of 2 µg/m^3 for airborne inorganic arsenic for any 15 minute period of the workday.

The new (August, 1978) Occupational Safety and Health Administration (OSHA) standard for airborne inorganic arsenic is 10 µg/m^3 TWA.

Current Levels of Exposure

A broad range of arsenic levels have been found in drinking water samples. In a U.S. Environmenal Protection Agency national study of residential tap water, 66.8 percent of the one time grab samples collected from 3,834 residences had arsenic levels greater than 0.1 µg/l. The average, minimum, and maximum levels of the samples with detectable arsenic were 2.37, 0.05, and 213.6 µg/l, respectively (Greathouse and Craun, 1978). In

1975 it was reported that 5 out of 566 samples collected from Interstate Carrier Water Supplies exceeded 10 µg/l and that the maximum level was 60 µg/liter (U.S. EPA, 1975). Well water samples collected during 1976 at 59 residences in a Fairbanks, Alaska suburban community had a mean arsenic content of 224 µg/liter with a range from 1.0 to 2,450 µg/l (U.S. Public Health Service, 1977). Moderately elevated levels of arsenic, 10 to 330 µg/l, are present in potable waters of some smaller communities in Nevada and California (Valentine, 1979). There have been a number of other reports of isolated instances of higher than usual concentration of arsenic in well waters (Goldsmith, et al. 1972; Feinglass, 1973; Morton, et al. 1976). The highest value reported in these studies was 21,000 µg/l in well water contaminated by arsenical grasshopper bait.

There is a wide diversity in the estimates of daily intake of arsenic in foods. Schroeder (1968) has estimated that the average diet provides an arsenic intake of about 1,000 µg/day. Arsenic in a sample institutional diet amounted to about 400 µg/day (Schroeder and Balassa, 1966). This lower level is attributed, at least partially, to the absence of seafood, a primary source of arsenic, in the institutional diet. In contrast to these levels, the World Health Organization (WHO) reported that average arsenic intakes for Canada, the United Kingdom, the United States, and France varied from 25 to 33 µg/day; specific values ranged from 7 to 60 µg/day (WHO, 1973).

According to Suta (1978), the levels of atmospheric arsenic in locations where major arsenic emitting sources are absent range from below the detection limit of 1 ng/m^3 to 83 ng/m^3 with an average of 3 ng/m^3. The annual average near major emission sources (copper, lead, and zinc smelters, cotton gins, pesticide manufacturers, and glass manufacturers) ranged from 3 ng/m^3 to 5,900 ng/m^3 with most below 290 ng/m^3. Assuming normal daily inhaled volumes of 21.2 and 11.1 cubic meters for men and women, respectively, the ranges of daily airborne arsenic exposures in uncontaminated areas are 760 ng and 11-921 ng for men and women respectively. In areas where arsenic emitting sources are located daily, inhaled exposure levels may be as high as 6,148 to 125,080 ng and 3,219 to 65,490 ng for men and women, respectively.

No quantifiable information was found concerning present levels of exposure from drugs or dermal contact.

Special Groups at Risk

Adverse effects have been demonstrated in all age groups of both sexes. Children may have an increased susceptibility to arsenic-induced CNS damage (Hamamoto, 1955; Okamura, et al., 1956; Yamashita, et al., 1972).

Basis and Derivation of Criterion

As described in the Carcinogenicity Section, a number of studies have shown that arsenic is important in the etiology of human cancers. Clinical, occupational, and population studies have demonstrated that both ingestion and inhalation exposures to arsenic compounds increase the risk of cancer induction in the tissues of the lung and skin and possibly other sites. There appears to be general agreement that arsenic is a human carcinogen, despite of the fact that there has been general failure to demonstrate this effect in any animal model. Hence, it is necessary to rely totally on human data rather than supplement it with appropriate animal toxicity and carcinogenic data. This limitation causes serious problems since animal studies are the only practical means to effectively evaluate relative toxicities, absorption rates, etc. for different compounds and routes of administration. Instead, these types of questions must be answered based on effects and observation of exposed populations recognizing the numerous unknowns (levels of arsenic and other environmental exposures, dietary patterns, genetic differences, etc.) and different routes of exposure.

The only study that relates levels of arsenic ingestion to skin cancer is the one conducted by Tseng (1968) in southwest Taiwan. He found a consistent dose response relationship between the exposure variable levels of arsenic in drinking water and age and skin cancer prevalence. Questions concerning comparability between the U.S. and Chinese populations must be raised since some areas in the U.S. have similar arsenic levels without the reported dermatological manifestations. It is very possible that major differences in dietary patterns (the Chinese diet is low in protein and fat) (Yeh, 1973), other environmental and/or occupational coexposures, socioeconomic status, etc. may account for the differences. However, since similar health responses have been observed in Antofagasta, Chile (Borgono and Greiber, 1972), Cordoba, Argentina (Bergoglio, 1964), German vineyard workers (Denk, et al. 1969), and those who ingest Fowler's Solution (Neubauer, 1947), it must be assumed that arsenic is at least one component of the environmental exposures responsible for the observed effects. Secondly, the clear dose response relationships both by length of exposure, as indicated by age, and by level of waterborne arsenic provide additional evidence that arsenic is at least one of the agents responsible for the observed effects. It seems quite unlikely that other environmental, occupational, or socioeconomic factors which might be responsible for variations in skin tumor incidence would have a similar gradient to the waterborne arsenic gradient. Hence it appears reasonable to use the Taiwan data as a basis for estimating a level which will not increase the lifetime risk of cancer by more than 1/100,000. It is recognized the calculated level may be quite conservative since the Taiwan experience may represent a worst case situation due to exposures and other agents, possibly dietary deficiencies.

The EPA Cancer Assessment Group has developed a mathematical prediction model for estimating an acceptable level based on the published Taiwan data (Tseng, 1977). Their material is included in Appendix I to explain the model and the calculated estimates.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Arsenic is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of arsenic in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of arsenic corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1) ng/l		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g grams fish and shellfish. (2)	0.22	2.2	22
Consumption of fish and shellfish only.	1.75	17.5	175

(1) Calculated by applying a relative risk model for epidemiology studies, as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document and as discussed in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Thirteen percent of the arsenic exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 44-fold. The remaining 87 percent of arsenic exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of arsenic, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding arsenic concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding arsenic concentrations.

Although total exposure information for arsenic is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assumed an incremental risk from ambient water exposure only.

The criterion as estimated by the methodology may appear unreasonably low. However, inorganic arsenic is clearly established as a human carcinogen including ingestion in drinking water. Further, negative findings in large population groups (Harrington, et al. 1980; Morton, et al. 1976; Southwick, et al. 1980) have been carefully evaluated by the Agency to check if the criteron predicts an incidence above what was found in these studies. The Agency concludes that the Taiwan experience is not invalidated by the lack of skin cancer incidence in areas of the United States where people are exposed to arsenic through drinking water.

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APPENDIX

Mathematical Prediction Model

Due to the stable population in a rural area along the southwest coast of Taiwan, the data collected by Tseng, et al. (1968) may be viewed as a lifetime feeding study where measured amounts of arsenic in well water are consumed by a study population of 40,421 individuals. Thus, this data may be used to predict the lifetime probability of skin cancer caused by the ingestion of arsenic.

A model estimating the cancer rate as a function of drinking water arsenic concentration was generated using the information in its published form, which is a summary of data collected by the investigators. If the original data had been available, a more exact mathematical analysis would have been possible.

Doll (1971) has suggested that the relationship between the incidence of some site specific cancers, age, and exposure level of a population may be expressed as:

$$(1)\ I(x,t) = vBx^{m}t^{v-1}$$

where x is the exposure level of a carcinogen, t is the age of the population, and B, m, v are unknown parameters.

However, the data collected by Tseng, et al. (1968) was obtained at one point in time, and since skin cancer has only a marginal effect on the death rate, the obtained rates may be viewed more accurately as the probability of having contracted skin cancer by time t. The relationship between this probability, often referred to as the cummulative probability density or prevalence, and the incidence or age specific or hazard rate may be expressed as:

$$(2)\ F(x,t) = 1 - \exp\left[\int_{0}^{t} I(x,s)\,ds\right]$$

Utilizing the suggestion of Doll (1971) for the form of the incidence rate, the prevalence may be expressed as:

$$(3)\ F(x,t) = 1 - \exp\left(-Bx^{m}t^{v}\right)$$

which is a Weibull distribution.

In Table 1, based on information in Tseng, et al. (1968), we have estimates of $F(x,t)$ for different age and exposure groupings for males.

To use this data, specific values for x and t had to be obtained for the intervals. Where the intervals were closed the midpoint was utilized. For the greater than 0.6 ppm group, the midpoint between 0.6 and the greatest recorded value 1.8 was taken, resulting in 1.2 ppm. For age 60 or greater, a value of 70 was utilized somewhat arbitrarily, being the same increase over the lower level as that in the other two age intervals. The values for (x,t) to relate to the prevalence estimates are shown in parentheses in Table 1.

From equation (3) it follows that:

$$(4)\ \ln(-\ln[1-F(x,t)]) = \ln(B) + m\ln(x) + v\ln(t)$$

which is multiple linear in form. Estimating the parameters by the usual least square techniques, we obtained the relationship:

$$(5)\ \ln(-\ln[1 - F(x,t)]) = 17.548 + 1.192\ln(x) + 3.881\ln(t)$$

which is an excellent fit having a multiple correlation coefficient of 0.986.

Equation (5) may be expressed as:

$$(6)\ F(x,t) = 1 - \exp[-10^{-7} \times 0.2429x^{1.192}\, t^{3.881}] =$$

$$= 1 - \exp[-H(t) \times 1.192]$$

If the coefficient $m \approx 1.192$ was in fact equal to 1, then for a given value of t equation (6) would be "one-hit" in form.

TABLE 1

Age - Exposure - Specific Prevalence Rates*

ppm[a]	20-39 (30)	40-59 (50)	≥60 (70)
0 - .29 (0.15)	0.0013	0.0065	0.0481
0.30 - 0.59 (0.450)	0.0043	0.0477	0.1634
≥0.6 (1.2)	0.0224	0.0983	0.2553

*Source: Tseng, et al. 1968

[a] Range given. Midpoint is in parenthesis.

To test this hypothesis (i.e., Ho: $m = 1$) the student "t" test is used, giving the result:

$$t_6 = \frac{1.192 - 1}{0.138} = 1.391$$

which is not significant at the 0.1 level. The value 0.138 is the standard error of m. Thus there is insufficient evidence to reject the hypothesis that the dose response relationship is "one-hit" even at the 0.1 level even though the standard error of the regression coefficient is quite small.

Fixing $m = 1$ we have the relationship:

$$(7)\ F(x,t) = 1 - \exp[-g(t)x]$$

Transforming this equation to its linear form and obtaining the least square estimates of B and v, we find that:

$$g\ (t) = \exp(-17.5393)\ t^{3.853}, \text{ where } B = 2.41423 \times 10^{-8},\ v = 3.853$$

In this case, the fit is still quite good as represented by a correlation of 0.971. The data used to obtain the estimates is shown in Table 2 and the goodness of fit is illustrated in Figure 1.

The function $F(x,t) = 1-\exp[-2.41423 \times 10^{-8} \times t^{3.853}]$, is the probability of contracting skin cancer by age t given that a individual had a life-time exposure to x ppm in his drinking water (and lived until age t).

In Appendix I of the CAG (1978) coke oven document, the lifetime probability of cancer in the presence of competing mortality was derived from the age-specific incidence rate. For the case where the cancer rate in the absence of exposure is near zero (as in this case where the skin cancer is of a rate form that was virtually unknown in other parts of Taiwan) the lifetime probability may be expressed as:

$$Q_2(\alpha) = Bx/(Bx+p^v)$$

TABLE 2

Data Utilized to Obtain Predictor Equation and Figure 1

ppm Arsenic	Age at Medical Examination	Skin Cancer Prevalence Rate		Transformed Skin Cancer Prevalence Rate	
		$F(x,t)$		$-\ln(-\ln[1-F(x,t)])= -17.5393 + 3.853\ln t+\ln x$	
x	t	Observed Rate	Expected Rate	Observed	Expected
0.15	30	0.0013	0.0031	6.64474	6.33160
	50	0.0065	0.0127	5.03269	4.36341
	70	0.0481	0.0455	3.00993	3.06695
0.45	30	0.0043	0.0053	5.44699	5.23299
	50	0.0477	0.0375	3.01849	3.26480
	70	0.1634	0.1304	1.72368	1.96834
1.20	30	0.0224	0.0141	3.78739	4.25216
	50	0.0983	0.0969	2.26844	2.28397
	70	0.2553	0.3110	1.22155	0.98751

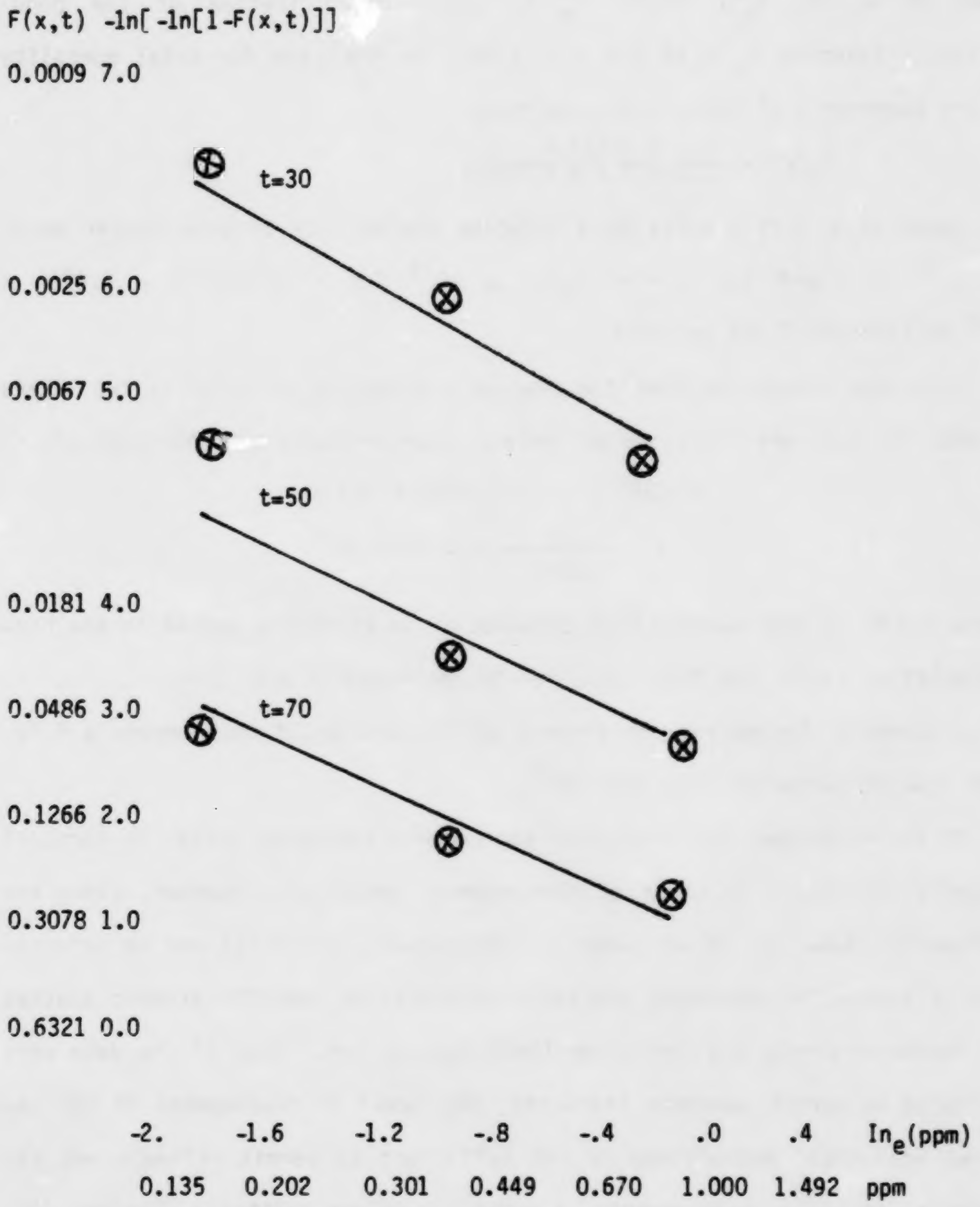

FIGURE 1

Relationship between Transformed Prevalence and log ppm Arsenic in Water, log age where $p^v = \ln 2\ t_m^v$, (where t_m is the median lifetime of the population). Assuming $t_m = 68$ and $v = 3.853$, is the same for total mortality as the appearance of skin cancer, we have:

$$Q_2(\alpha) = \frac{2.41423\ x}{2.41423\ x + 6.02793}$$

The level of x that results in a lifetime probability of skin cancer equal to 10^{-5} is found by solving $Q_2(\alpha) = 10^{-5}$ for x giving $X = 2.4969 \times 10^{-5}$ mg/liter or 0.025 μg/liter.

Under the assumption that the average consumption of water is two liters in both the U.S. and Taiwan we estimate a water criteria concentration of:

$$2(.025) = C(2 + 0.0065 \times 44) \text{ or}$$

$$C = \frac{.05}{2.2860} = 0.0219\ \mu g/l$$

Where 0.0065 is the average fish consumption in kilograms and 44 is the bioaccumulation factor for fish (supplied by Don Mount of U.S. EPA).

A standard for waterborne arsenic of 22 ng/l would thus insure a lifetime risk of cancer of less than 10^{-5}.

It is recognized that inorganic and organic compounds differ in terms of toxicity and likely in terms of carcinogenic potential. However, since the recommended level is to be based on carcinogenic potential and no information is available concerning the relationship(s) of specific arsenic species and cancer a single all inclusive limit must be set. Even if the data were available to permit separate standards, the level of development of the required analytical methodology is not sufficient to permit reliable and repeatable speciation measurements, a necessity before setting a standard (Dr. Irgolic, Texas A&M University, personal communication).

For comparative purposes, the Stockinger and Woodward (1958) method was applied to the present and proposed airborne arsenic standards to compute comparable waterborne arsenic levels.

American Conference of Governmental Industrial Hygienists:

1. Existing threshold limit value - time-weighted average - 500 $\mu g/m^3$

$$\frac{500\ \mu g}{m^3} \times \frac{10\ \text{m3}}{\text{work day}} \times \frac{5\ \text{work days}}{\text{week}} \times 20\%\ \text{absorption} = 5{,}000\ \mu g/\text{week}$$

$$\frac{5{,}000\ \mu g}{\text{week}} \times \frac{1\ \text{week}}{7\ \text{days}} \times \frac{1}{2\ \text{liters}} \times \frac{\text{Allowed}}{80\%\ \text{absorption}} = 446\ \mu g/l$$

Applying the recommended safety factor of 100 the comparable drinking water limit is 4.46 µg/l.

2. Proposed threshold limit value - time-weighted average - 50 $\mu g/m^3$

$$\frac{50\ \mu g}{m^3} \times \frac{10\ \text{m3}}{\text{work day}} \times \frac{5\ \text{work days}}{\text{week}} \times 20\%\ \text{absorption} = 500\ \mu g/\text{wk}$$

$$\frac{500\ \mu g}{\text{week}} \times \frac{1\ \text{week}}{7\ \text{days}} \times \frac{1}{2\ \text{liters}} \times \frac{\text{Allowed}}{80\%\ \text{absorption}} = 44.6\ \mu g/l$$

Applying the recommended safety fator of 100 the comparable drinking water limit is 0.45 µg/l.

Occupational Safety and Health Administration:

1. Eight-hour average - 10 $\mu g/m^3$

$$\frac{10\ \mu g}{\text{week}} \times \frac{10\ \text{m3}}{\text{work days}} \times \frac{5\ \text{work days}}{\text{week}} \times 20\%\ \text{absorption} = 100\ \mu g/\text{week}$$

$$\frac{100\ \mu g}{\text{week}} \times \frac{1\ \text{week}}{7\ \text{days}} \times \frac{1}{2\ \text{liters}} \times \frac{\text{Allowed}}{80\%\ \text{absorption}} = 8.93\ \mu g/l$$

Applying the recommended safety factor of 100, the comparable drinking water limit is 0.09 µg/l.

Assuming that the absorption factors (air-20 percent, water-80 percent) and methods recommended by Stockinger and Woodward (1958) are reasonable and that the safety of 100 is appropriate, it is clear that the recommended water standard is even more restrictive than the air standards. The differences are likely due at least partially to variations in extrapolation methods and levels of acceptable risk.

It is of interest to see what cancer risk would be associated with an air exposure equivalent to the recommended water standard of 0.02 µg/l. If we make the following assumptions:

(1) Total daily average absorbed arsenic from water is:

$0.8 \times 0.02\ (2 + 0.0065 \times 44) = 0.0366$ µg, where 80 percent is the absorption rate.

(2) The breathing rate is 1 m^3/hr and 20 percent of the arsenic is absorbed.

Then, the air concentration, X, required to obtain the same absorbed amount of arsenic is:

$$0.2 \times 24 \times X = 0.0366\ \mu g \text{ or}$$
$$X = 0.008\ \mu g/m^3$$

From the 1978 CAG report on the risk associated with airborne arsenic the lifetime cancer risk associated with X $\mu g/M^3$ of arsenic in the air is estimated to be:

$$P = 3.418 \times 10^{-3} X$$

If instead of basing our risk on the most sensitive study we use the geometric mean of the three studies, the lifetime cancer risk would be:

$$P = 1.95 \times 10^{-3} X$$

The risks associated with $X = 0.008$ are thus 2.73×10^{-5} and 1.56×10^{-5}. Thus, if our water standard was based on the geometric mean of the human epidemiological air studies, it would be 0.013 µg/l instead of 0.02 µg/l, which is a remarkably consistent result.